ANNALS OF THE RHEUMATIC DISEASES

Ann. rheum. Dis. (1955), **14**, 325.

EXPERIENCE WITH CORTISONE IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS*

REPORT OF A CO-OPERATIVE STUDY CONDUCTED BY A COMMITTEE OF THE AMERICAN RHEUMATISM ASSOCIATION†

(RECEIVED FOR PUBLICATION OCTOBER 6, 1955)

At a meeting of the American Rheumatism Association held in Chicago in June, 1952, a preliminary report was presented of the co-operative clinical trial of ACTH, cortisone, and aspirin in the treatment of rheumatic fever, sponsored by the Medical Research Council of Great Britain and the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association (Joint Report, 1955). This report aroused such interest that it was decided to consider undertaking a similar study of cortisone in the treatment of rheumatoid arthritis. The feasibility of such a study was discussed by an *ad hoc* committee consisting of Drs Joseph J. Bunim, Gideon K. deForest, Richard Freyberg, William Kammerer, Donald Mainland, Currier McEwen, Felix Moore, Charles Ragan, William Robinson, Edward Rosenberg, Charles L. Short, Charles Slocumb, Charley J. Smyth, and Morris Ziff. The difficulties encountered in the co-operative study of rheumatic fever were weighed, as were the still greater difficulties inherent in a similar study of such a chronic and variable disease as rheumatoid arthritis. It was agreed that it would not be advisable at that time to embark on a "forward-moving" study of new cases—as had been done in the rheumatic fever study—, but that it would be worth while to undertake a retrospective analysis of data already accumulated in a selected group of clinics.

Support for the study was provided by the Arthritis and Rheumatism Foundation. Miss Claire Lingg was appointed staff statistician and Mrs. Esther Bigus co-ordinating secretary. Letters were written to the chiefs of a large number of selected clinics in the United States and Canada, of whom the following joined the project:

Dr. Arthur W. Bagnall, *Vancouver General Hospital, Vancouver, B.C., Canada.*
Dr. Walter Bauer and Dr. Charles L. Short, *Massachusetts General Hospital, Boston, Mass.*
Dr. Theodore B. Bayles, *Robert B. Brigham Hospital, Boston, Mass.*
Dr. Paul J. Bilka, *University of Minnesota Hospital, Minneapolis, Minn.*
Dr. Gideon K. deForest, *Grace-New Haven Community Hospital, New Haven, Conn.*
Dr. Ephraim P. Engleman, *Veterans Administration Hospital and Regional Office, San Francisco, Cal.*
Dr. Dwight C. Ensign, *Henry Ford Hospital, Detroit, Mich.*
Dr. Richard Freyberg, *Hospital for Special Surgery, New York, N.Y.*
Dr. Wallace Graham, *Sunnybrook Hospital, St. Michael's Hospital, and Toronto General Hospital, Toronto, Canada.*
Dr. Edward Hartung, *Fourth (N.Y.U.) Division, Bellevue Hospital, New York, N.Y.*
Dr. Philip Hench and Dr. Charles Slocumb, *Mayo Clinic, Rochester, Minn.*
Dr. W. Paul Holbrook, *Southwestern C. & R.I., Tucson, Ariz.*
Dr. Joseph L. Hollander, *Hospital of the University of Pennsylvania, Philadelphia, Pa.*
Dr. William Kammerer, *New York Hospital, New York, N.Y.*
Dr. John Lansbury, *Temple University Hospital, Philadelphia, Pa.*
Dr. Melvin Levin, *Veterans Administration Hospital, Los Angeles, Cal.*
Dr. James J. Lightbody, *The Harper Hospital, Detroit, Mich.*
Dr. L. Maxwell Lockie, *Buffalo General Hospital, Buffalo, N.Y.*
Dr. Currier McEwen and Dr. Morris Ziff, *Third (N.Y.U.) Division, Bellevue Hospital, New York, N.Y.*
Dr. Charles Ragan, *Faulkner Clinic, Columbia Presbyterian Medical Center, New York, N.Y.*
Dr. William Robinson, *University Hospital, Rackham Arthritis Research Unit, Ann Arbor, Mich.*
Dr. Edward F. Rosenberg, *Michael Reese Hospital, Chicago, Ill.*
Dr. Richard T. Smith, *Benjamin Franklin Clinic, Philadelphia, Pa.*
Dr. Charley J. Smyth, *Colorado General Hospital, Denver, Col.*
Dr. Robert M. Stecher and Dr. Anita Ausenbachs, *Cleveland City Hospital, Cleveland, Ohio.*
Dr. Otto Steinbrocker, *Lenox Hill Hospital, and Hospital for Joint Diseases, New York, N.Y.*

* This study was supported by a grant from the Arthritis and Rheumatism Foundation.

† The Committee responsible for preparing the report consisted of: Dr. Currier McEwen (*Chairman*), Dr. Richard Freyberg, Dr. William Kammerer, Miss Claire Lingg, Dr. Donald Mainland, Dr. Charles Ragan, Dr. Charles Short, and Dr. Morris Ziff.

Objectives

(1) To obtain information that would enable the American Rheumatism Association (or other group) to decide whether a controlled comparison of various treatments of rheumatoid arthritis is feasible, and if so, how it could best be planned;

(2) To ascertain the experience of certain clinics, during a certain time period, in the treatment of rheumatoid arthritis with cortisone;

(3) To look for differences in response that might appear to be related to certain features in the patients or to the mode of treatment;

(4) To look for differences between the reports of different clinics regarding outcome and to seek for hints of possible explanations;

(5) To form an impression of the facilities of the clinics and of their suitability for possible co-operation in a subsequent controlled comparison of different treatments.

Method

Early in the study the following criteria for admitting patients to the project were agreed on:

(1) Patients must have straightforward rheumatoid arthritis of peripheral joints.

(2) Cortisone must have been the main therapeutic agent used.

(3) The arthritis must have been present for at least 6 months before the administration of cortisone.

(4) Only patients would be included who had been observed by the participating physician for a period of at least one year since the initiation of cortisone, and the patient must have received cortisone continuously,* in doses not smaller than 15 mg. daily, with the following exceptions:

(*a*) dosage stopped because of sustained remission;
(*b*) dosage stopped because of toxicity;
(*c*) dosage reduced or discontinued temporarily for observation of patient's response;
(*d*) dosage discontinued because of inadequate benefit to the patient.

The criteria adopted by the American Rheumatism Association (Steinbrocker, Traeger, and Batterman, 1949) were used:

Stage of Disease

I—Early (osteoporosis, but no destructive radiological changes; no nodules or tenosynovitis).
II—Moderate (slight cartilage or bone destruction; nodules and tenosynovitis may be present in this and more advanced stages).
III—Severe (cartilage and bone destruction, extensive muscle atrophy, subluxation, ulnar deviation).
IV—Terminal (Stage III plus ankylosis).

Class of Functional Capacity

I—Completely normal.
II—Adequate (conducts normal activity despite handicap).
III—Limited (performs few or none of the duties of usual occupation or self care).
IV—Incapacitated (little or no self-care).

Grade of Response

I—Complete remission (no positive laboratory or systemic signs of rheumatoid activity; irreversible anatomical changes may persist).
II—Major improvement (minimal residual joint swelling and activity may persist).
III—Minor improvement (joint inflammation only partially resolved).
IV—No improvement or worse (laboratory and clinical data same or worse).

* For the purposes of the study, "continuously" includes those patients who may have stopped cortisone temporarily, but in whom the intent was continuous treatment.

In order to make the collection of data as comparable as possible, special printed forms were adopted for the recording of information (opposite).

Limitations of the Method.—From the outset it was clear that a retrospective analysis of this sort would have certain drawbacks; and other limitations became apparent as the study progressed. Such an analysis, for example, does not permit detailed recording of new observations during the study, but must make use of data already recorded by clinicians who made their original entries with no idea that they would subsequently become part of a statistical investigation. Furthermore, many of the data had been recorded on the original clinic charts several years before the study began and the workers who transferred these data to the official forms (Figure) were not in many instances those who had recorded the original observations. This difficulty was made greater by the fact that the stage and class of disease and the grade of response were recorded at clinic visits in only a few clinics, so that observers who knew the patients only slightly, if at all, often had to translate clinic notes into terms of the official criteria.

It should constantly be borne in mind that this study was primarily designed to ascertain the amount and kind of information that was available. It did not, therefore, meet the requirements of a definitive study. These requirements and a discussion of the limitations of the survey method are presented in the companion article (Mainland, 1955) which immediately follows this report. In the analysis, attention was confined to those statements and figures that had the appearance of being most reliable. If, however, it had been possible to make, at each clinic, a proper study of the numerous factors influencing the figures and other statements that were received, some of the estimates and inferences presented here might have been different.

The Sample

Forms were collected for a total of 608 patients from the various clinics, of which 62 had to be eliminated because of incompleteness or obvious unreliability, leaving 546 which form the basis of this analysis. The question of bias in selection of patients was obviated by including only patients from those clinics which submitted data on their total patient population which met the criteria. The patients all had been under observation for at least one year since the start of cortisone therapy and many had been under treatment and observation for longer periods between 1949, when cortisone first became available, and May 1, 1953, the closing date for submitting forms for inclusion in the analysis. Some patients had been under treatment throughout this period, but others only during the early or later parts of it. Clearly, it was a period of change in methods of selecting patients for cortisone and in schedules of dosage.

A.R.A. COOPERATIVE STUDY OF CORTISONE THERAPY IN RHEUMATOID ARTHRITIS

Name	Sex	Date of birth (*month - day - year*)	Institution	Patient's Chart No.

1. DIAGNOSIS

Rheumatoid arthritis (peripheral)	Y	N
Spondylitis (spine and sacro-iliac only)	Y	N
Spondylitis with hip and/or shoulder involvement	Y	N
Spondylitis with peripheral joints	Y	N
Psoriasis present	Y	N
Psoriasis with terminal I-P involvement	Y	N

2. START OF CORTISONE THERAPY *

month · *day* *year*

(*Encircle which*)
Before Menopause
During Menopause
After Menopause
No Record

8. ONSET OF DISEASE

month *year*

9. ONSET OF THIS ATTACK

month *year*

10. OTHER DISEASES - *at start of Cortisone**

Tuberculosis**	Y	N
Diabetes mellitus**	Y	N
Hypertension	Y	N
Peptic ulcer**	Y	N
Psychoneurosis**	Y	N
Other**	Y	N

11. JOINTS INVOLVED *at start of Cortisone**

(*Encircle which*)

Hand Wrist Elbow
Shoulder Foot
Ankle Knee Hip
Spine Jaw

3. DOSAGE - Mgs. (approximate daily average by months)

1	2	3	4	5	6	7	8	9	10	11	12
13	14	15	16	17	18	19	20	21	22	23	24
25	26	27	28	29	30	31	32	33	34	35	36

12. PREVIOUS THERAPY

			Result (*improved, same, worse*)
Gold	Y	N	
Cortisone	Y	N	
Corticotropin	Y	N	
Other**	Y	N	

13. CONCOMITANT THERAPY

			Helpful (*yes, no, doubtful*)
Gold	Y	N	
Intra-articular Cpd. F	Y	N	
Corticotropin	Y	N	
Salicylates	Y	N	
Butazolidin	Y	N	
Other**	Y	N	

4. Result of Treatment

	Stage	Class	Grade	Wt. (lbs.)	B.P.	# ESR	Hb.	Hct.
Before Cortisone			xxxx					
After 2 weeks								
1 month								
3 months								
6 months								
9 months								
12 months								
15 months								
18 months								
21 months								
24 months								
27 months								
30 months								
33 months								
36 months								

E.S.R. Method:

14. SIDE EFFECTS

	Date appeared	Duration	Cortisone (*continued, reduced, stopped*)
Glycosuria			
Fluid retention**			
Psychosis**			
Peptic ulcer**			
Thrombosis**			
Pathological fracture			
Infection**			
Masking of infection**			

Moonface	Y	N	NR
Acne	Y	N	NR
Hirsutism	Y	N	NR
Striae	Y	N	NR
Emotional instability	Y	N	NR
Redistribution of fat	Y	N	NR
Menstrual irregularity	Y	N	NR
Excess fatigability	Y	N	NR

5. CORTISONE STOPPED PERMANENTLY

Date stopped

month *day* *year*

Reason (*encircle which*)

Remission Partial remission Inadequate benefit
Worse Toxicity** Other**

6. NODULES *at start of Cortisone**

Present Y N

Change during treatment (*encircle which*)

Unchanged Increased
Decreased Disappeared
No record

7. PSORIASIS *at start of Cortisone**

Present Y N

Change during treatment (*encircle which*)

Unchanged Increased
Decreased Disappeared
No record

15. FOLLOW UP

Patient still under observation Y N

Patient died Y N _____
month *day* *year*

Cause of death _____

Patient left study Y N _____
month *day* *year*

Reason _____

*** By participating clinic. ** Amplify on reverse side.**

(*Signed*) _____ M. D.

Date: _____

Answer every question. Leave no blanks. Where the answer is unknown, write "NR" (No Record).

All patients, of course, met the requirements noted above (p. 326). These were considered essential to ensure the inclusion of only genuine cases of rheumatoid arthritis. However, the requirements themselves introduced several difficulties. For example, a patient in whom cortisone had been tried previously and found either ineffective or "toxic" would probably not get into the series.

Age at Onset of Disease.—Four patients were under 5 years of age at the onset of their disease, and three patients were over 80. In only slightly more than 4 per cent. was the age at onset of disease under 15. The frequency of first episodes rose rapidly from age 15 to age 30, remained high to age 60, and then fell rapidly. Fully three-quarters of the patients had experienced the onset of disease between the ages of 25 and 60 years.

It is not possible to determine accurately the age incidence of a disease from data such as these, because one does not know the number of persons at a given age in the general population from which these patients were drawn who might have attended these clinics had they been attacked. Therefore, we have chosen not to show the foregoing figures, and those in the following paragraphs, in graph form lest they appear to possess an accuracy which would be unwarranted.

Age at Start of Cortisone Therapy.—Three patients were under 5 years of age at the start of treatment and four were over 80. Only 3 per cent. of the males and 5 per cent. of the females were under 20 and most of them were between 35 and 60 years of age. This doubtless reflects in part the relative rarity of the disease before maturity, but probably also the rarity of children in many of the clinics.

Sex.—Of the 546 patients, 37 per cent. were males and 63 per cent. females.

Duration of Disease at Start of Cortisone Therapy.—The duration of disease ranged from less than one to more than 24 years. Duration was less than 4 years in roughly 25 per cent., less than 8 in roughly 50 per cent., and more than 12 in roughly 25 per cent.

Previous and Concomitant Therapy.—The question forms provided space for the clinic physicians to record previous and concomitant therapy as well as their own and the patient's appraisal of benefit induced. All patients had received some form of drug therapy before entering the study. Gold compounds had been used in roughly 60 per cent. and short courses of corticotropin or cortisone in about 30 per cent. Most had received salicylates. Similarly, during the present period of study, gold compounds were given concomitantly to about 20 per cent. of the patients, phenylbutazone to about 20 per cent., and salicylates to about 70 per cent. The information obtained regarding the apparent effects of these agents was too incomplete to justify presentation, except that the great majority of patients and physicians considered concomitant salicylates helpful.

Analysis of the Data

Disposition of Patients at End of Study.—At the end of the study, 432 patients were still under observation, of whom approximately 60 per cent. were still receiving cortisone. The remaining 114 patients of the original 546 were no longer available. Of these, 29 (5 per cent. of the total) had died, and 85 (16 per cent. of the total) had been lost to the study for a variety of reasons: about one-quarter because of dissatisfaction resulting from "toxicity" or lack of benefit, about one-third because of transfer to care by other physicians or movement to another community, and about one-fifth because of failure to co-operate. It is probably safe to assume that, save for the ten who moved to other communities, most of these patients were not satisfied with the results.

Table I (opposite) shows certain data on the 29 patients who died. Probably some of these deaths were related to the cortisone therapy, whereas such a relationship appears most unlikely in others. However, information regarding all possible untoward effects of cortisone is still too meagre to decide which of these deaths were and which were not influenced by therapy.

Dosage.—During the first few weeks or months of cortisone therapy, the dose used is relatively large in many clinics and rather wide variations in the amount given are frequent from week to week. In analysing the dosage schedules employed, therefore, the first 3 months of treatment were excluded. In 43 per cent. of the patients the average daily dose after the third month of treatment was not more than 50 mg.; conversely, in 57 per cent. it was more than 50 mg. Since the more seriously ill patients would be expected to require the larger doses, it was not surprising to find that those taking more than 50 mg. daily tended to receive cortisone longer than those taking 50 mg. or less. Conversely, it was not unexpected to find that considerably more of the patients receiving the smaller doses went into remission (23 per cent.) than of those receiving the larger doses (7 per cent.).

Undesirable Occurrences during Cortisone Therapy.—The untoward events in patients receiving cortisone are usually referred to as "effects" of treatment. For the purposes of this report it has seemed preferable to call these "occurrences", because it is not always possible to be certain whether or not the hormone was the cause. In most instances, however, it is reasonable to suppose that these undesirable occurrences were, in fact, related to the therapy.

For purposes of this discussion the undesirable occurrences were separated into those considered of major significance and those of minor importance. This is, of course, an arbitrary distinction and not all readers will agree on the category into which the

TABLE I

DEATHS WHILE UNDER OBSERVATION

(29 Patients)

Cause of Death		Sex	Age at Death	Death Occurred: While on Cortisone	Death Occurred: After Cortisone was Stopped (mths)	Duration of Cortisone Therapy (mths)	Reason for Stopping Cortisone
Malignant rheumatoid arthritis		F	48	—	4	20	Worse
		F	53	x		20½	
Disseminated lupus erythematosus and cerebral thrombosis		M	49	—	2½	1	Inadequate benefit
Acute bacterial endocarditis		M	60	x		19	
Cancer	Transverse colon	F	50	—	1	26	Operation for cancer
	Reticular cell sarcoma of mandible with widespread metastasis	M	42	x		22	
Circulatory Disease	Myocardial infarction	M	56	x		6	
		M	56	—	2–3	2	Peptic ulcer—inadequate benefit
		M	62	x		17	
	Cardiac decompensation	F	69	x		3	
		M	80	—	1	8	Fluid retention—probably myocardial failure
		M	64	—	12	13	Inadequate benefit
		F	42	—	2	11	Phlebitis, pathological fracture
	Cerebral haemorrhage	F	86	x		18	
		F	77	x		15	
		F	77	—	½	20	Congestive failure, collapsed vertebra
Pneumonia		F	72	—	14	4	Cardiac failure, hypochloric alkalosis
		M	59	x		18	
		M	60	—	1½	10	Thrombosis and pulmonary infarction
		M	59	x		8	
*Tuberculosis		M	58	—	5	1	Pulmonary tuberculosis
Pancreatitis		F	68	—	4 days	26	Pancreatitis
Bowel infarction secondary to diffuse periarteritis nodosa		M	56	—	1½	3	Acute manic-depressive psychosis
Infarcted ileum with peritonitis		M	54	x		10	
Bacteraemia		F	48	—	4	16	Bleeding duodenal ulcer; pathological fracture of vertebra
Anaesthetic death with shock		M	50	—	2 days	14	Haematemesis
Accident—fire		F	72	—	3	11	Haematemesis—neoplasm stomach
Suicide		F	60	x		8	
Unknown or no record		F	42	x		5	No further record

* No history of tuberculosis at start of cortisone.

specific occurrences are placed. Notably, for example, many would include glycosuria among the minor incidents, and others might consider excessive fatigability a major symptom of danger.

Table II lists the "major" undesirable occurrences. It will be noted that almost half of the patients exhibited one or more and that, as would be expected, the incidence was greater in patients receiving more than 50 mg. cortisone daily.

Table III lists the "minor" undesirable occurrences. Again, the incidence was greater in the group receiving more than 50 mg. cortisone daily, but, as in the case of the "major" occurrences, some

TABLE II

MAJOR UNDESIRABLE OCCURRENCES

Major Undesirable Occurrences	Per cent. of 546 Patients	Per cent. of 232 Patients receiving 50 mg. or less	Per cent. of 314 Patients receiving more than 50 mg.
Glycosuria	8·6	8·2	8·9
Fluid retention	24·3	19·8	27·7
Psychosis	2·4	2·2	2·5
Peptic ulcer	6·6	4·4	8·3
Thrombosis	5·5	2·7	7·6
Pathological fracture	3·3	0·9	5·1
Infection	11·0	7·7	13·4
Masking of infection	0·9	0·4	1·3
None	54·1	63·3	47·4

TABLE III

MINOR UNDESIRABLE OCCURRENCES

Minor Undesirable Occurrences	Per cent. of 546 Patients	Per cent. of 232 Patients receiving 50 mg. or less	Per cent. of 314 Patients receiving more than 50 mg.
Moonface	57·7	40·5	70·5
Acne	10·8	9·5	11·8
Hirsutism	15·7	15·5	15·9
Striae	5·6	5·2	6·0
Emotional instability	20·1	14·6	24·2
Redistribution of fat	21·6	9·9	30·2
Menstrual irregularity*	37·6	30·0	43·6
Excess fatigability	17·9	12·4	21·3
None	28·0	40·5	18·8

* Per cent. of 138 pre-menopausal patients.

appeared to be as apt to occur with the smaller as with the larger doses.

Two cautionary comments must be made regarding the data in Tables II and III. First, it is probable that the rates of, at least, the major untoward incidents are lower than they would have been if only patients who had never previously taken cortisone had been included in the study; because those who had previously manifested severe undesirable changes would be less likely to appear in the survey than those who had used cortisone without difficulty. Second, because of the varied lengths of time of treatment and observation, the percentages of undesirable occurrences can be taken as greater than would have been found in patients treated and observed for exactly 12 months, but less than if treatment of all patients had continued to 24 months or longer.

An attempt was made to analyse the effects of duration of treatment and of age on the rates of major undesirable occurrences. It was the opinion of the committee that the data probably were not sufficiently reliable to warrant presentation in tabular form; however, certain comments may be made. There appeared to be no consistent relationship between duration of treatment and the appearance of major undesirable occurrences, with the possible exception of pathological fractures which occurred more frequently in the patients treated longer. As regards the age of the patient at the time of treatment, there was only one instance each of glycosuria and of spread of infection among 23 patients under the age of 20 years, and none of the other major untoward incidents. Because of the small number of patients in that group these figures cannot be considered statistically significant. They are, however, in agreement with the usual experience that untoward occurrences are relatively infrequent in children. After the age of 20, the patient's age appeared to have little bearing on the rates of occurrences with the exception of pathological fractures and, possibly, of peptic ulcer. Pathological fractures, as would be expected in view of the increase in osteoporosis in post-menopausal women and in elderly males, were found more often in the older patients (the actual figures being none under age 20, 0·6 per cent. in the 20 to 44 year age group, 3·3 per cent. in the 45 to 64 year age group, and 9·8 per cent. in the 51 patients over 65). Conversely, peptic ulcer was noted in 9·3 per cent. of patients between 20 and 44 years of age, in 6·3 per cent. of those between 45 and 64, and in only 2 per cent. of those over the age of 64. These figures do not necessarily represent the true incidence of such occurrences in patients receiving cortisone.

Taking the major undesirable occurrences as a whole, it is of interest to note that, save for the patients below the age of 20 (only 4 per cent. affected), the rates among the patients in the three older age groups were almost identical—50, 46, and 49 per cent. respectively.

Effect of Treatment on Nodules and Psoriasis.—Rheumatoid subcutaneous nodules were recorded as present in 159 patients (29 per cent.). These increased in number or size or both during treatment in 21, and remained unchanged in 79; they decreased in 37 patients, but disappeared in only nine. There was no record of the result in the remaining thirteen patients. Thus, there appeared to be no relationship between the course of the nodules and the administration of cortisone.

Psoriasis was reported in 27 (5 per cent.) of the 546 patients. As in the case of nodules, there appeared to be no relationship between cortisone therapy and the course of the cutaneous lesions.

Effect of Treatment on Arthritis

The motivating purpose of the entire study, of course, was to see what might be learned from the various clinics regarding the effects of cortisone on the articular and systemic manifestations of rheumatoid arthritis.

Table IV (opposite) summarizes the grade of improvement in 546 patients at the end of observation if they were still on cortisone, or at the time cortisone was stopped. The time that cortisone was stopped was taken for purposes of recording as the last date before stopping cortisone on which observations of grade of improvement were reported on the survey form. Since the latter was done at 3-monthly intervals, this length of time would be the maximum possible interval between the date of the observation of grade of improvement and the date of stopping cortisone.

TABLE IV

GRADE OF IMPROVEMENT AT END OF OBSERVATION IF STILL ON CORTISONE, OR AT TIME CORTISONE WAS STOPPED

At Start of Cortisone		Number of Cases	Grade of Improvement (Per cent.)				
Stage	Class		I	II	III	IV	N.R.*
I or II	I or II	110	13	44	32	9	2
I or II	III or IV	108	12	38	29	19	2
III or IV	I, II, III or IV	328	3	27	45	23	2

* No record.

It should be pointed out that the grades of improvement noted correspond to different periods of treatment for different individuals, these intervals being in some cases as short as a few weeks and in other cases as long as 36 months. Also, since cortisone was stopped because of toxicity in the case of some patients, the grades of improvement given apply in a proportion of the cases to patients who at the time of evaluation were exhibiting toxic reactions to cortisone serious enough to require stopping the drug. This, however, would not be expected to influence the grade of improvement. Finally, it is likely that at the time of the last evaluation before stopping cortisone, the dosage was being tapered off in a number of the patients; so that even though cortisone had not been stopped, it has been reduced in dosage sufficiently to render these patients susceptible to relapse of symptoms.

It is readily apparent from the Table that the greatest improvement occurred in those patients whose disease was less far advanced.

Interclinic Variations.—It has been intended to subject the data from the total group of patients to more detailed analysis. However, appraisal of the forms submitted for the individual patients revealed such wide variations for the different clinics that such an approach was invalid. Table V illustrates the differences in the distribution of patients by grade of therapeutic response at the end of 12 months of treatment with cortisone in thirteen of the clinics. These clinics were selected by excluding those that presented data for fewer than ten patients in Stages 3 and 4 at the beginning of treatment and also those from which the data were in any other respect unsatisfactory. Patients in Stages 3 and 4 were selected for this detailed analysis because they were more numerous than those in the milder stages of disease. The number of patients varied from 53 in Clinic C to ten in Clinics E and Z. Percentages in Grades 1 and 2 are shown separately in Table V to illustrate the rarity with which Grade 1 was assigned, but the percentage in these two grades are then pooled to show the proportion of more favourable results. These varied from none to 71 per cent. in the thirteen clinics (mean 30 per cent.). Conversely, the proportion of patients with unsatisfactory results (Grades 3 and 4 and those in whom cortisone was stopped because of inadequate benefit) varied from 22 to 93 per cent. in the different clinics (mean 60 per cent.). If to these are added those patients whose cortisone was stopped because of undesirable occurrences, the unsatisfactory results increase to 29 to 100 per cent. in the various clinics (mean 70 per cent.). The number of undesirable occurrences considered sufficiently serious to require stopping cortisone ranged from none among 53 patients in three clinics to 30 per cent. in another clinic (mean 10 per cent.).

Even when allowance is made for the relatively small numbers in some of the clinics, the differences are highly significant, the probability of chance

TABLE V

DIFFERENCES IN DISTRIBUTION OF PATIENTS BY GRADE OF IMPROVEMENT 12 MONTHS AFTER START OF CORTISONE IN THIRTEEN CLINICS
INITIAL STATUS—STAGES 3 AND 4 IN ALL CLASSES

(The values are percentages rounded to the nearest 1 per cent.)

Clinic		A	B	C	D	E	G	H	L	M	N	P	Q	Z	Mean
Number of Patients		16	9	53	30	10	13	34	14	18	24	13	23	10	—
Status after 12 Months	Grade 1	6	—	2	—	—	—	6	—	—	8	—	4	—	2
	Grade 2	19	34	34	7	30	31	26	71	39	38	—	13	20	28
	Total	25	34	36	7	30	31	32	71	39	46	—	17	20	30
	Grades 3 and 4 and Inadequate Benefit*	56	54	55	93	70	69	65	22	44	50	85	65	50	60
	Toxic†	19	12	9	—	—	—	3	7	17	4	15	18	30	10
	Total	75	66	64	93	70	69	68	29	61	54	100	83	80	70
Total		100	100	100	100	100	100	100	100	100	100	100	100	100	100

* Inadequate Benefit = Cortisone stopped permanently because it was judged to confer inadequate benefit, or patient became worse.
† Toxic = Cortisone stopped permanently because of undesirable occurrences.

occurrence being only slightly greater than 0·001 (by the χ^2 contingency test). In order to learn whether there was any obvious factor that might help account for these differences, the data in Table V were analysed from the following standpoints:

(1) Percentage of female patients at each clinic;
(2) Percentage of private patients;
(3) Average age at onset of the attack of rheumatoid arthritis that formed the subject of this survey;
(4) Average interval between original onset of disease and start of cortisone therapy;
(5) Average date of start of cortisone therapy (this factor was examined because of the possibility of changing therapeutic customs or types of patients selected over the 3-year period;
(6) Average number of joints involved at the start of treatment;
(7) Percentage of patients in Stage 3 at start of treatment;
(8) Percentage of patients in Classes 1 and 2 at start of treatment;
(9) Average number of specified forms of concomitant therapy per patient;
(10) Percentage of patients given gold as concomitant therapy;
(11) Percentage of patients treated with salicylates in addition to cortisone.

For each of these eleven items a relationship with the performance index (percentages in Grades 1 and 2) of the same clinic at 12 months was sought by dot diagram, and if the diagram showed any possibility of a relationship a correlation coefficient was calculated. The method is crude, but, with one exception, there was no suggestion of a correlation. The one exception was a negative correlation (rank correlation coefficient −0·53) between the percentage in Grades 1 and 2 and the average number of joints involved at the start of cortisone therapy. That is, the smaller the average number of joints involved per patient, the higher was the percentage of patients in the more favourable groups.

The possibility was also borne in mind that in some clinics the patients may have had more "active" rheumatoid arthritis, or arthritis less susceptible to change by any form of therapy. For example, some clinics may have chosen for cortisone therapy chiefly patients who had responded poorly to other forms of treatment, whereas in other clinics cortisone may have been the first therapeutic agent selected. Unfortunately, differences of this type are not necessarily reflected in stage and class of disease and hence are not readily distinguished in the forms from which the statistical analyses were derived.

In spite of these possible factors, no simple explanations were found which would satisfactorily account for all the variations between clinics. A very plausible suggestion is that the differences lay largely in the interpretations of the various clinic physicians—differences in interpretation of the criteria of stage and class of disease and of grade of response, in judgment as to severity of disability, undesired occurrences, and the like. The incidence of unsatisfactory benefit plus "toxic effects" sufficient to require stopping cortisone reported by the various clinics illustrates this point well. As shown in Table V, it varied between 29 per cent. in one clinic and 100 per cent. in another. It would appear probable that such variations represented differences in the judgment of the physicians rather than in the reactions of the patients.

Status of Patients at Intervals after Start of Cortisone

More Seriously Affected.—One consequence of the significant differences between clinics was that simple summation of the patients from all the clinics to produce overall percentages would distort the picture by giving weight according to the numbers of patients contributed to the survey by the respective clinics. In the preparation of material for the subsequent Tables, therefore, the unweighted averages were used. For example, in Table V, the thirteen percentages for Grade 2 were summed and divided by thirteen to give the mean (28 per cent.) in the last column; and this was entered in the 12-months column of Table VI (opposite). The other columns of that Table and those which follow it were produced in the same way.*

Table VI shows the distribution of patients by grade of response at intervals after the start of cortisone treatment for those patients from the thirteen clinics who had an initial status of Stages 3 and 4 (all classes) at the start of the study. Regarding the number of patients, the deficiency at 2 weeks as compared with 6 months is due to the absence of a record of grade in fifteen patients, but the record for this group at the next observation time (one month) was almost identical with the record of those patients from the same clinic whose records were complete; therefore, there is no reason to suspect that bias has been introduced. The decrease in numbers after 12 months is due chiefly to the stipulation that 12 months be the minimum period for observation. Fewer patients had been under observation for 18 months, fewer still for 24 months, and so on. The diminishing totals, therefore, are for the most part not true losses; *i.e.* patients who started treatment early enough to contribute to the 18-, 24-, or 30-month data but who failed to continue under observation. Although there were eighteen

* Some further details of calculation are discussed by Mainland (1955).

TABLE VI

DISTRIBUTION OF PATIENTS BY GRADE OF RESPONSE AT INTERVALS AFTER START OF CORTISONE TREATMENT
INITIAL STATUS—STAGES 3 AND 4, ALL CLASSES

Mean (Unweighted) Percentages for Thirteen Clinics

Time after Starting Cortisone (months)		0·5	6	12	18	24
No. of Patients	Total	254	269	267	222	186
	Range per clinic	9–53	10–53	9–53	3–50	3–48
Grade of Response	Grade 1	2	1	2	1	2
	Grade 2	49	30	28	30	26
	Total	51	31	30	31	28
	Grades 3 and 4 and Inadequate Benefit	48	63	60	55	51
	Toxic	1	6	10	14	21
	Total	49	69	70	69	72
	Total	100	100	100	100	100

true losses after 24 months, examination showed that no reasonable disposition of these patients, if their status at 24 months had been known, would have had much effect on the conclusions to be drawn from the Tables. The same was not true regarding losses among the less severe cases, discussed later.

Table VI shows that, if we may assume that Grades 1 and 2 indicate a favourable response and the other grades an unfavourable response, the responses in terms of averages of the thirteen clinics appear to be favourable and unfavourable in about equal proportions at 2 weeks, and then in a fairly steady ratio of 3 : 7 for the next 2 years. The data at the end of 30 months showed some decrease in the average percentage in the "favourable" group. However, the number of contributions from many of the clinics had become so small by that time that it would be unwise to draw conclusions from the 30-month data, which are not included in Table VI.

As regards the fairly steady ratio of 3 : 7 during the 2-year period, inspection of the raw data revealed that this was not due to any two-way flow between the favourable and unfavourable groups, but mostly to a tendency for patients to remain in one or the other of these broad groups.

Table VII presents a similar analysis of the same patients as those in Table VI, but in terms of their functional class. A marked improvement is seen by the end of the second week of treatment compared with the status immediately before the start of cortisone. At 6 months the ratio of more favourable outcome (Classes 1 and 2) to less favourable outcome is about 1 : 1, and thereafter there appears to be a slight but fairly steady decline to about 2 : 3 at the end of 2 years. The data are not broken down for the individual thirteen clinics as was done for grades in Table V. At the end of 30 months the percentages were essentially the same as at 24 months. Again, however, the number of patients contributed by some clinics by that time was too small to warrant drawing conclusions. As with grades, the interclinic variation was large; for example, at 12 months the percentage in the favourable group varied from 20 per cent. in one clinic to 75 per cent. in another.

Less Seriously Affected.—The data for patients

TABLE VII

DISTRIBUTION OF PATIENTS BY FUNCTIONAL CLASS AT INTERVALS AFTER START OF CORTISONE TREATMENT
INITIAL STATUS—STAGES 3 AND 4, ALL CLASSES

Mean (Unweighted) Percentages for Thirteen Clinics

Time after Starting Cortisone (months)		At Start of Treatment	0·5	6	12	18	24
Number of Patients			254	269	267	222	186
Functional Class	Class 1	1	5	5	7	5	5
	Class 2	19	53	47	41	41	35
	Total	20	58	52	48	46	40
	Classes 3 and 4, Inadequate Benefit, Toxic	80	42	48	52	54	60
Total		100	100	100	100	100	100

TABLE VIII

PERCENTAGES OF PATIENTS SHOWING A FAVOURABLE (GRADE 1 OR 2) RESPONSE AT INTERVALS AFTER START OF CORTISONE TREATMENT

The mean (unweighted) percentages for patients in Stages 3 and 4 are transferred from Table VI, which shows the number of clinics and patients

Initial Status	Time after Starting Cortisone (months)			
	0·5	6	12	Interclinic Variations at 12 mths
Stages 1 and 2, Classes 1 and 2	76	57	44	0–83
Stages 1 and 2, Classes 3 and 4	61	45	37	0–70
Stages 3 and 4 (from Table VI)	51	31	30	0–71

Data for Stages 1 and 2, Classes 1 and 2, are from twelve clinics; total patients, 73 (3–11 per clinic).
Data for Stages 1 and 2, Classes 3 and 4 are from ten clinics; total patients, 63 (2–10 per clinic).

less seriously affected (those in Stages 1 and 2 at the start of the study) were divided into two groups according to their initial functional class: *i.e.* those in Classes 1 and 2, and those in Classes 3 and 4. Unweighted averages, obtained as in Table VI, are shown in Table VIII. Reliable conclusions were scanty, however, because:

(*i*) The numbers of patients per clinic were small, varying from two to eleven;

(*ii*) The true losses, as defined above, amounted to eleven out of 92 patients by the end of 24 months and cast doubt on the validity of conclusions drawn from the patients who remained under observation.

Therefore, in order to minimize the effect of lost patients, attention in Table VIII is confined to the first 12 months. As would be expected, it appears that the percentage of favourable results varies inversely as the initial status. It is seen also that by the end of 12 months of cortisone treatment the average percentage of favourable results in all three groups is between 30 and 45 per cent.

Table IX presents a similar comparison of milder and more severe cases with respect to functional class. The familiar improvement immediately after the start of treatment is followed by a decline, but even at the end of 12 months there was an average of close to 75 per cent. of favourable results in the milder cases, and of close to 50 per cent. in the more severe cases.

Changes in Individual Patients.—In the discussion of Table VI, it was mentioned that the degree of improvement remained fairly steady after 6 months and that this steadiness was due chiefly to the tendency for individual patients to remain at the same level of improvement, rather than to a two-way flow of deterioration and improvement. This was fairly obvious from inspection of the individual data sheets, and was confirmed by more precise examination.

In one clinic from which the data appeared very reliable, 38 patients initially in Stages 3 and 4 provided data for 24 months. None of them showed a better grade of response at 24 months than at 12, 66 per cent. were in the same grade, and 34 per cent. had deteriorated. When the same patients were analysed by functional class, the same relationships were found, except that 8 per cent. of the patients had been assigned a more favourable class at 24 months than at 12.

In a similar analysis of 61 milder cases (initial Stages 1 and 2) from twelve clinics, 3 per cent. showed a better grade at 24 months than at 12, 72 per cent. remained in the same grade, and 25 per cent. deteriorated. There were no significant differences between the various clinics in these figures.

These data suggest that improvement attained by the end of 12 months may be expected to continue for at least another year in 60 to 70 per cent. of

TABLE IX

PERCENTAGES OF PATIENTS SHOWING A FAVOURABLE (CLASS 1 OR 2) RESPONSE AT INTERVALS AFTER START OF CORTISONE TREATMENT

The mean (unweighted) percentages for patients in Stages 3 and 4 are transferred from Table VII (number of clinics and patients as in Table VI)

Initial Status	Time after Starting Cortisone (months)				
	At Start of Treatment	0·5	6	12	Interclinic Variations at 12 mths
Stages 1 and 2, All Classes	57	85	80	73	44–86
Stages 3 and 4, All Classes (from Table VI) ..	20	58	52	48	20–75

Data for Stages 1 and 2 are from twelve clinics; total patients, 125 (4–21 per clinic).

patients. However, the limitations of the method of study and the small number of patients do not justify a firm conclusion.

Discussion

In addition to the aim of obtaining information about the course of rheumatoid arthritis in patients under treatment with cortisone, an important purpose of this study was to learn whether a controlled comparison of various forms of treatment of this disease is feasible. In this connexion the most important feature was probably the revelation of the great differences in the data of the different clinics. For evaluation of cortisone therapy it has sometimes been proposed that a comparison be made of a cortisone-treated series of patients with a series treated before the days of cortisone. This "previous series" method is always perilous, and how perilous it may be is well illustrated by the present survey, where large differences between cortisone-treated series are revealed.

A co-operative scheme of a "forward-moving" clinical trial, *e.g.* comparison of cortisone and salicylates, for example, would doubtless reduce the interclinic differences by standardization of methods and criteria; but it is improbable that it would remove serious interclinic differences entirely. Therefore, it would be unrealistic to expect that direct pooling of the data from all the participating clinics would be permissible. Samples of the present size might well be adequate to show the superiority of one or another treatment; but even the largest individual samples in the present series would not give precise estimates of the benefits of any one treatment in any one clinic.

The large number of patients in this survey who received other agents as concomitant therapy, and the urgent desire of many patients to receive cortisone, suggests that there might be considerable difficulty in obtaining sufficient participants for an adequate co-operative, standardized, controlled trial in clinics in the United States. From the quality of the data, however, it appears probable that it would be possible to select certain clinics or physicians as appropriate participants in a controlled clinical trial or in some other type of study.

Summary and Conclusions

A statistical analysis has been made of the course of rheumatoid arthritis in a group of patients treated with cortisone in 29 co-operating clinics and observed for 1 to 3 years between 1949 and 1953. Certain of the data reported were derived from the entire sample of 546 patients, whereas others which required more detailed analysis were derived from a smaller sample of approximately half that number from thirteen clinics which submitted the largest individual samples.

The survey was designed primarily to reveal the amount and kind of information available throughout the country and did not meet the requirements of a definitive study, but the estimates and inferences are based on those statements and figures that had the appearance of being the most reliable.

In three-quarters of the patients the onset of disease had occurred between the ages of 25 and 60 years. Females comprised 63 per cent. of the group and males 37 per cent.

In roughly 25 per cent. of the patients, rheumatoid arthritis had been present for less than 4 years, in 50 per cent. less than 8 years, and in 25 per cent. more than 12 years.

Most of the patients had received therapy before the study began, and some also received concomitant therapy with agents other than cortisone during the period of the study; but valid conclusions as to the benefit of such treatments could not be drawn.

At the end of the period of study, 432 of the 546 patients were still under observation, and of these 60 per cent. were still receiving cortisone. Of the other 114 patients, 29 (5 per cent.) had died, and 85 (16 per cent.) had been lost to the study.

Undesirable occurrences of major significance were seen in 46 per cent. of the 546 patients, and minor undesirable occurrences in 72 per cent.

Rheumatoid subcutaneous nodules were present in 29 per cent., and psoriasis in 5 per cent. No significant relationship was found between the course of these lesions and treatment with cortisone.

Wide differences in the progress of patients under cortisone were reported by the various clinics. These great differences which appeared to arise chiefly from differences in interpretation and judgment on the part of the various clinic physicians, made necessary special statistical treatment of the data in order to arrive at justifiable conclusions.

Among the patients more severely affected by the disease (Stages 3 and 4 when the study began), the ratio of favourable to unfavourable results at the end of 2 years was 3 : 7 in terms of grade of response, and 4 : 6 in terms of improvement in functional class. In the more mildly affected patients (Stages 1 and 2 when the study began), the proportion of favourable results was larger. In all groups improvement was more favourable in terms of functional class than in terms of grade of response (as defined by the American Rheumatism Association; Steinbrocker and others, 1949).

The limitations of this type of therapeutic survey are discussed more fully by Mainland (1955).

REFERENCES

Medical Research Council and American Heart Association (1955). "Joint Report by the Rheumatic Fever Working Party of the M.R.C. and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease." *Circulation*, **11**, 343; *Brit. med. J.*, **1**, 555.
Mainland, D. (1955). *Annals of the Rheumatic Diseases*, **14**, 337.
Steinbrocker, O., Traeger, C. H., and Batterman, R. C. (1949). *J. Amer. med. Ass.*, **140**, 659.

Expérience avec la cortisone dans le traitement de l'arthrite rhumatismale

Rapport d'une enquête collective dirigée par un comité de l'*American Rheumatism Association*

RÉSUMÉ

On a procédé à une enquête statistique sur l'évolution de l'arthrite rhumatismale chez un groupe de malades traités par la cortisone et suivis pendant 1 à 3 ans entre 1949 et 1953 dans 29 cliniques participant à l'enquête. D'entre les données présentées ici, certaines proviennent du groupe entier de 546 malades; d'autres, ayant exigé une analyse plus détaillée, dérivent environ de la moitié de ce nombre et se basent sur des renseignements fournis par 13 cliniques disposant de plus grands lots de cas.

Cette enquête a été entreprise avant tout pour connaître le genre et la quantité des renseignements disponibles dans le pays, sans donc créer des conditions réquises pour une analyse précise, mais les calculs et les déductions se basent ici sur ces constatations et chiffres qui ont la meilleure apparence d'exactitude.

Chez trois quarts des sujets la maladie a débuté entre l'âge de 25 et de 60 ans. Le groupe comprenait 63% de femmes et 37% d'hommes.

Chez environ 25% des sujets, l'arthrite rhumatismale était présente depuis moins de 4 ans, chez 50% moins de 8 ans et chez 25% moins de 12 ans.

La plupart des malades a été traitée avant le commencement de cette enquête, et certains d'entre eux ont été traités, en plus de la cortisone, par d'autres moyens au cours de la période d'enquête, mais on ne peut pas tirer de conclusions valables sur le bénéfice de tel traitement.

A la fin de l'enquête, sur les 546 malades, 432 se trouvaient encore sous observation et 60% d'entre eux recevaient toujours de la cortisone. D'entre les 114 restants, 25 (5%) étaient morts et 85 (16%) se sont trouvés en dehors de l'enquête pour des raisons variées.

On a observé des effets secondaires majeurs chez 46% des 546 malades et des mineurs chez 72%.

Des nodules rhumatismaux sous-cutanés étaient présents chez 29% et le psoriasis chez 5%. On n'a pas trouvé de rapport significatif entre l'évolution de ces lésions et le traitement par la cortisone.

En comparant les rapports de diverses cliniques on a trouvé de grandes différences dans le progrès des malades traités par la cortisone. Ces différences, attribuables surtout à l'interprétation et au jugement des médecins des cliniques, ont demandé une élaboration statistique spéciale des données pour pouvoir arriver à des conclusions justifiables.

Chez des malades graves (stade 3 et 4 au temps du commencement de l'enquête) au bout de 2 ans les résultats favorables et défavorables étaient en proportion de 3 : 7 du point de vue de la réaction thérapeutique graduée et de 4 : 6 du point de vue fonctionnel. Chez les malades benins (stade 1 et 2 au début de l'enquête) la proportion des résultats favorables était plus grande. Dans tous les groupes le critère fonctionnel indiquait une amélioration plus prononcée que le critère de la réaction thérapeutique (selon la définition de l'*American Rheumatism Association*; Steinbrocker *et coll.*, 1949).

On discute plus amplement les limitations d'une enquête thérapeutique de ce type dans une maladie de genre d'arthrite rhumatismale dans l'article suivant (Mainland, 1955).

Experiencia con la cortisona en el tratamiento de la artritis reumatoide

Informe de un estudio cooperativo dirigido por una comisión de la *American Rheumatism Association*

SUMARIO

Se procedió a un análisis estadístico respecto a la evolución de la artritis reumatoide en un grupo de enfermos tratados con cortisona en 29 clínicas participantes y seguidos durante uno a tres años entre 1949 y 1953. De los datos presentados aquí, algunos proceden del grupo entero de 546 enfermos; otros, habiendo necesitado un análisis más detallado, vienen de un numero aproximadamente dos veces menor, ofrecido por 13 clínicas con los mayores lotes de casos.

El primer objeto de esta investigación fué el averiguar el tipo y la cantidad de información disponible en el país sin crear condiciones para un estudio de precisión, pero los cálculos y las deducciones aquí se basan sobre informes y cifras que ofrecen la mayor apariencia de exactitud.

En los tres cuartos de los sujetos la enfermedad había empezado entre la edad de 25 y 60 años. El grupo comprendió un 63% de mujeres y un 37% de hombres.

En cerca de 25% de los enfermos la artritis reumatoide había existido desde menos de 4 años, en 50% desde menos de 8 años y en un 25% desde menos de 12 años.

La mayoría de los enfermos obtuvo tratamiento antes de empezar esta investigación; algunos recibieron, además de la cortisona, otra terapia durante el período de investigación; no se puede sin embargo sacar conclusiones válidas respecto al beneficio de tales tratamientos.

Al cabo de la investigación, de los 546 enfermos, 432 encontrábanse todavía bajo observación y el 60% de ellos seguía recibiendo cortisona. De los demás 114, 25 (5%) murieron y 85 (16%) encontráronse por varias razones fuera de la investigación.

Ocurrencias nocivas mayores se observaron en el 46% y menores en el 72%.

Nódulos reumáticos subcutáneos se vieron en un 29% y psoriasos en un 5%. No se notó relación significativa entre la evolución de estas lesiones y el tratamiento con la cortisona.

Al comparar los informes de varias clínicas se observaron grandes diferencias en el progreso de los enfermos tratados con cortisona. Estas diferencias debidas principalmente a la interpretación y al juicio de los médicos de las clínicas, exigieron una elaboración estadística especial de los datos para poder llegar a conclusiones justificables.

En los enfermos graves (período 3 y 4 al tiempo de empezar la investigación) al cabo de 2 años la proporción de los resultados favorables y desfavorables fué de 3 : 7 según los criterios de la respuesta terapéutica graduada y de 4 : 6 desde el punto de vista de la mejoría funcional. En los enfermos benignos (período 1 y 2 al empezar la investigación) la proporción de los resultados favorables fué mayor. En todos los grupos el criterio funcional indicó resultados más favorables que el criterio de la reacción terapéutica graduada (definidos por la *American Rheumatism Association*; Steinbrocker y col., 1949).

Se discuten más detalladamente las limitaciones de tal investigación terapéutica en enfermedades del tipo de artritis reumatoide en el artículo siguiente (Mainland, 1955).

Ann. rheum. Dis. (1955), **14**, 337.

USE OF CASE RECORDS IN THE STUDY OF THERAPY AND OTHER FEATURES IN CHRONIC DISEASE

I. PLANNING THE SURVEY

BY

DONALD MAINLAND

From the Department of Medical Statistics and Study Group on Rheumatic Diseases, New York University College of Medicine

(RECEIVED FOR PUBLICATION OCTOBER 6, 1955)

Experiments and Surveys

Probably few physicians now fail to appreciate the need for a properly conducted experiment if there is doubt whether a treatment is beneficial, or if the relative merits of two treatments are not known. The essential features of such a controlled therapeutic or clinical trial are easily stated:

(1) Allocation of treatments (*e.g.* two drugs or drug and placebo) to patients by an automatic random technique, such as random numbers;

(2) "Double blindfold" method, whereby patients are kept unaware of the differences in treatments, and those who assess the results are unable to identify patients with treatments.

The conduct of the experiment is not easy (Daniels, 1951; Green, 1954; Herdan, 1955; Hill, 1951b, 1952; Mainland, 1954b), and it is natural to ask what information can be gained by a non-experimental method, such as a survey of case records, supplemented, where possible, by follow-up studies (interviews or mail questionnaires). In the comparison of treatments, Densen and others (1952) have shown that even under exceptionally favourable conditions a case record survey can produce very misleading conclusions. Although the records often contain the results of "trial and error" experiments, these cannot be utilized as experiments because they do not insure the control of hidden bias.

Possible Uses of Case Record Surveys

There are, however, two other common problems:

(1) Estimation of the amount of benefit obtainable from a treatment already known to be beneficial;

(2) Estimation of the deleterious effects of such a treatment.

The exploration of the possible value of case records in such problems was one purpose of the American Rheumatism Association's Co-operative Study of Cortisone Therapy in Rheumatoid Arthritis, described elsewhere in this issue (p. 325) and hereafter referred to as the "Study". This Study should by no means be taken as a model. It was made extensive in order to ascertain the quality and the amount of response possible in a forward-going survey or in a therapeutic trial, but it retains the features of a preliminary exploration, including many defects that would have to be removed before even a pilot study (a small-scale dress rehearsal) could be started. Nevertheless, its scope and faults render it useful in an attempt to answer three questions:

(1) What can be safely inferred, from a case record survey, regarding the benefits and drawbacks of a particular treatment, especially in a complex chronic disease?

(2) What reliable information can such a survey give regarding aetiology or clues thereto, and inter-relationships of phenomena, between diseases and within one disease?

(3) How far can a clinician conduct such a survey, even on his own records, without the help of an epidemiological statistician?

The third question is vital, because such statisticians, even medical statisticians of any kind, or biological statisticians with time for medical projects, are far too few to help in more than a very small fraction of current researches. This problem was examined recently (Mainland, 1954a) from the point of view that every investigator is already to some extent his own statistician, but that many investigators need to improve their skill by grasping certain general principles and by acquiring a few simple techniques of design and analysis appropriate to their particular projects. This would limit the scope and complexity of many inquiries and eliminate some entirely, but the general quality of such work would improve.

A clinician who desired such skill in case record surveys could obtain some general help from text-

books (where principles are often enmeshed in arithmetic), from the literature of public health and industrial medicine (Cochran, 1951, 1953; Cornfield, 1951; Doll, 1951; Dorn, 1953; Greenberg, 1953; Hansen and Hurwitz, 1951; Hill, 1951a, 1953; Sartwell and Merrell, 1952), and from a report by the American Public Health Association's Committee on Sampling Techniques (1954). In the clinical field are introductory discussions by Asher (1954), Mainland and Herrera (1954a) and White (1953), whose article on sampling in medical research is very illuminating.

The present article, and one now in preparation on analysis of data, are intended to meet the need for more detailed guidance. They do not attempt to enumerate all the errors in the Cortisone Study (or rather, the features that would have been errors in a final survey); nor is it implied that all the errors mentioned were committed in that Study.

Nine Questions for Use in Planning

If treated with latitude, nine questions (Mainland, 1952, p. 12), found useful in criticizing reports, are helpful also in planning investigations. The questions, and their implications in case record surveys, are as follows:

(1) *Who?*—Persons responsible for the original observations and for the survey.
(2) *Why?*—The purposes of the survey.
(3) *What?*—The population sampled.
(4) *Where?*—Location and environment (*e.g.* of a clinic and its patients).
(5) *When?*—Time factors.
(6) *How?*—Methods of clinical observation and of survey.
(7) *How much?*—Measurement. (In the broad sense of assessing results, this is covered by Question 6.)
(8) *How many?*—Enumeration (numbers of patients and observations).
(9) *Why?*—Why did this happen?—Causal relationships.

Looking at this list, a clinician might well say: "All I wish to do is take stock of my experience with a certain treatment up to date, and find the percentages of patients improved, unchanged and worse. Must I consider in detail nine questions before doing this simple arithmetic?" The best answer would be: "What, precisely, would the percentages tell you?" Before replying he could profitably read (in full or in extensive quotations—Mainland, 1952, p. 13) an article by a perceptive surgeon on "The Use of Experience" (Ogilvie, 1949), and he might then seriously doubt the value of any such percentages, laden with multifarious bias. The nine questions are designed to show:

(1) How far such pessimism is justified,
(2) How forethought can reduce biases, which can be defined here for reference as "things that make a sample different from what it purports to be".

The notion that a survey, giving only "approximate" results, needs less care than a first-class experiment is erroneous. Particularly, it needs clear thinking throughout, and muddled thinking is common (Asher, 1954).

Persons Responsible for Observations and Survey

The effects of personalities on data and inferences are best discussed under *Methods*, but anyone who contemplates sharing in a survey should ask himself if he has enough time to do his part properly, and what his attitude will be.

Time Required.—There must be ample time for *thought*, for frequent personal consultation (not merely by letter or telephone) of all participants, and for detailed supervision of all assistants' work.

> Time is hard to estimate, but it may be mentioned that in this Department, when a clinical or laboratory colleague estimates the time required by a statistician to study a problem (without any computation) the estimate must often be multiplied by 10.
>
> Experience in the Cortisone Study and other surveys suggests that, because of clinicians' numerous other duties, at least 2 years should be allowed for a definitive survey designed to answer no more than five questions from a hundred pre-existing case records in one clinic. Certainly no less time would be needed for a *preliminary exploration* in a proposed co-operative study involving half a dozen clinics situated within a few travelling hours of each other.

Attitude.—The investigator should ask such questions as the following:

(*i*) Shall I be impeded in research by my need, in clinical practice, to be definite, helpful, optimistic, anxious for positive results?
(*ii*) Do I wish to hunt for bias, though it may mean discarding the whole survey?
(*iii*) When there is equal doubt regarding the validity of various results, shall I be more likely to accept, and propose publishing, a result that agrees with my previous impressions, rather than one which disagrees with them?
(*iv*) Am I inclined to brush aside, as too complex, subtle, sophisticated, or academic, a bias-causing mechanism that I do not understand?
(*v*) Am I inclined to react likewise to methods of analysis that I do not understand?
(*vi*) Shall I, a laboratory worker or statistician, fail to appreciate the difficulties of clinical research?*

* The New York University Department of Medical Statistics is peculiarly fortunate in not having to depend solely on recollected clinical experiences for its awareness of difficulties in research on patients. It meets the difficulties directly in its own *x*-ray investigations.

Purposes of the Survey

Two general purposes of case record surveys should be kept distinct:

(1) To increase experience regarding individual patients. Although called "anecdotal", this method of learning is not negligible. The reports of such surveys should, however, omit percentage frequencies, averages, and other estimates.

(2) To evaluate experience—the so-called "statistical" method—the subject of this article.

Before beginning an evaluational survey the investigator should express its purpose quite specifically. For every question that he intends to put to the data he should prepare a skeleton Table or statement, for example:

Result	Number of Cortisone-Treated Patients
Improved	?
Unchanged	?
Worse	?
Total	?

As planning proceeds, each term in the Table will have to be defined precisely; the Table itself may be modified, and it will probably be multiplied to show results by different criteria, such as Grade and Class.

It will be noted that the Table avoids the *post hoc propter hoc* fallacy committed in the Cortisone Study data sheet, which asked for "Results of Treatment", and in the official titles of the A.R.A. Grades ("Grades of Response to Therapy"). Even members of the Cortisone Study Committee caught themselves forgetting to allow for concomitant therapy, undetectable factors, and the natural fluctuations in the disease.

The investigator is not an archivist, but intends to use the information obtained—to be able to say, for example: "If I have a patient like those in the Table, and treat him in the same way, his chances of being in a better condition at the end of 12 months are about 30 per cent."; or again, if a co-operative survey revealed that only about 10 per cent. of moderately severe arthritics improved under cortisone, this would strengthen the rheumatologists' efforts to find something better. Therefore, since his purpose is practical, the investigator should at the outset, and throughout the planning, ask: "Shall I have enough patients to make my estimate of practical value?" This question is discussed later under *Confidence Limits*.

Definition of the Population

Any therapeutic study, whether by experiment or survey, is based on an assumption which has made medical practice possible, and has thereby been justified—the assumption that future patients will be sufficiently like the observed patients to make the results of the study applicable. That is, the sample is assumed to be representative of a fairly constant population. The investigator cannot define the population fully, but he should define it and its segments (subpopulations) as fully as he can. Otherwise, his estimates will mislead him and may perplex him by differing from other observers' estimates. He should note carefully what the definitions imply regarding the risk of bias in generalization.

Definition by Selection of Patients.—The Cortisone Study was conducted on the patients of rheumatic disease specialists and, with few exceptions, on patients affected only in the peripheral joints.

The samples would rarely include patients in whom cortisone, prescribed previously by other physicians, had been manifestly useless or very toxic, because after such a history a physician at one of the clinics in the Study would rarely try cortisone again. Therefore, as compared with the general population of rheumatoid arthritics, the patients would presumably possess three characteristics:

(1) A higher ratio of potential successes for cortisone treatment.

(2) A higher proportion of cases treated soon after onset, because cases of longer duration would have had a longer time during which they could have demonstrated the failure of cortisone, and thus have excluded themselves from the Study (6 months' minimum period, discussed below, would counteract this tendency to an undeterminable extent).

(3) A higher proportion of cases treated early in the period covered by the Study (1950-1952), just after cortisone had become available.

Very important was the selection introduced by two stipulations:

(1) Presence of arthritis for at least 6 months before cortisone administration—an effort to reduce the number of mistaken diagnoses, but tending to exclude successful cases.

Many of these would be mild cases, and even if they had been included their records should have been examined separately, because many of them go into remission, even without treatment. The automatic exclusion of cases of very recent onset, however, made it impossible to answer the question: "What happens to a severe case treated by cortisone within 6 months of onset?" Moreover, 6 months is an arbitrary dividing line.

(2) Observation for at least one year after the start of cortisone therapy—desirable to show how many such cases were available, but excluding an unknown number who had stopped attending a

clinic because they felt much better or because they were dissatisfied.

Any restriction can be placed on the class of patients surveyed, provided that:

(1) it is not ambiguous,
(2) it will give useful results,
(3) the results are not extrapolated beyond the subpopulation so defined.

In a final survey the restrictions imposed in the Study would impair the usefulness of the results by risk of bias —if, for instance, at a different time or place the factors responsible for loss of patients were different, or if a different proportion of severe cases were treated in the first 6 months. To avoid this, all cortisone-treated cases should be included, but different categories (possible subpopulations) could be studied separately (*e.g.* patients treated within a few weeks of first symptoms; diagnosis doubtful; diagnosis reversed during treatment).*

Definition by Patients' Characteristics.—Severity of disease at start of treatment is the most obvious basis for subdivision of the original population, and it is here that rheumatoid arthritis presents its major difficulties: difficulty of accurate diagnosis; lack of uniform diagnostic standards; and lack of reliable criteria of status and progress. Until better methods have been discovered, the patient's history, inaccurate though it may be, must play an important part in the physician's decision regarding the episodic or sustained character of the disease (Ragan, 1955).

Other subdivisions of the population, as by sex and age, will be discussed in the article on analysis. It should be noted here, however, that such subdivision is justified simply by the knowledge, or likelihood, that separate estimates are more applicable to their respective subpopulations than are pooled estimates. It does not imply profound causal relationship. Thus, females in a certain age group may, at a certain clinic, do better under treatment than females of other ages or males of the same age, simply because of a local socio-economic or occupational difference.

Definition by Therapy.—In the Cortisone Study the population comprised "cortisone-treated patients" with certain specifications (*e.g.* that cortisone must have been the main therapeutic agent, that a minimum daily dose of 15 mg. should have been continuous, with certain exceptions, including reduction or discontinuance of dosage for observation). These stipulations would be too arbitrary and complex for a final survey, in which records of all cortisone-treated patients (or all those in a well-defined class, such as adults) should be collected. Then, if division according to minimal dosage or continuity of treatment were desired, the rules should be made suitable to cover data from all the clinics.

Therapy of a chronic disease is, quite rightly, multiple, and assignment of rank may be very difficult. In rheumatoid arthritis, for example, when does aspirin (taken with or without the physician's knowledge) cease to be an occasional painkiller and become an anti-rheumatic treatment concomitant with cortisone?

When the administration of a drug is followed by improvement and no serious side-effects it will usually be continued, and the drug will be called the main (or sole) agent. Again, if there is no doubt about the physician's intention to continue the drug as the sole agent unless he is induced or compelled to stop it for such reasons as toxicity, inadequate benefit, or loss of the patient, such patients would clearly qualify for the survey.

Many cases, however, are not clear cut. A patient is started on Drug A, but receives from time to time another drug, B, either as part of the routine or because he seems to need additional help. At a certain time he appears to benefit greatly from Drug B; therefore its dose may be increased, while Drug A is cut in dosage or even stopped, temporarily or permanently. The process may be reversed, according to the patient's response; then a third drug, C, perhaps newly on the market, may be tried.

To eliminate from the survey such ambiguous cases, or all cases that received more than one drug, would give obviously biased estimates of that drug's efficacy. Dosage level gives little help in selecting the main therapy, because x mg. of Drug A daily for 2 months, without Drug B, is not equivalent to the same amount along with Drug B.

In the Cortisone Study no questions were asked regarding the grounds for stating that cortisone was the main therapeutic agent, and this may have been, in general, a safe procedure. However, one physician, who administered multiple therapy, stated that he had submitted records only of patients in whom he was convinced that the therapeutic response was due to cortisone, and this raised two questions that would have to be answered before his data could be used in a final survey:

(1) Would the record of a patient, receiving the same therapy, have been submitted if he or she had not shown a response?
(2) Would the lack of response have prompted the use of another drug, and thus have automatically excluded the patient's record from the survey?

Many patients in the Study had received concomitantly drugs other than cortisone, and, not infrequently, benefit was recorded. Therefore some of the responses, recorded at 3-month intervals, must have been due partly to those drugs. Even full information on times and doses would have permitted only partial, and somewhat speculative, separation of these effects from the cortisone effects.

* If a diagnosis is reversed at autopsy, the clinical diagnosis should be retained, for treatment is not based on a *post-mortem* diagnosis. (Densen and others, 1952).

The Study disregarded physiotherapy because most patients receive it, much or little. A final survey could not neglect it, because of its effects on functional capacity; and no therapy of a psychological kind can be overlooked, even in a survey of a predominantly physical disorder.

To cope with the complexity of therapy, perhaps the best skeleton Table would have heading and side-heads such as the following:

PATIENTS STARTED ON CORTISONE—CONDITION AT 12 MONTHS

(1) Treated by cortisone alone, or with concomitant treatment which had been administered, not because of inadequacy of cortisone, but as part of a routine, or for reasons other than the arthritis.
(2) Received concomitant treatment because cortisone was considered insufficient.
(3) Stopped cortisone because of inadequate benefit.
(4) Stopped cortisone because of toxicity.
(5) Lost because of progress of the arthritis.
(6) Lost from other causes and from unknown causes.

The body of the Table would contain numbers of patients for each side-head, and these could be expressed as percentages of the total. Group 5 would contain patients who died from the disease, and also other patients, such as those who became bedridden and unable to attend the clinic. Other losses (Group 6) will be discussed more fully later. This group might be subdivided in various ways, but it should contain those who went into remission and were lost before the end of 12 months.

Only in Group 1 would it be wise to record the status of patients, including those who had stopped cortisone because of remission, but were still under observation at 12 months. Group 2 is a lesser degree of Group 3, and to show the status of its patients would offer too great temptation for illicit comparison with Group 1.

In the final analysis the Grades, or other subdivisions, in Group 1 would each show a percentage of total patients, and the percentages in Groups 2 to 5 could, if desired, be pooled to show the proportion in whom cortisone had failed, partly or wholly.

Unless it is possible, objectively and without ambiguity or risk of bias, to classify patients as mainly on one treatment from the beginning, such a heading as "Cortisone-Treated" has little meaning. A clinician could more logically say:

> In my clinic cortisone is used largely, but not exclusively or on all patients. What is the condition of all patients 12 months after treatment is started, each patient having been treated as appeared best at the time?*

* Implicitly included here as part of the treatment is the physician himself.

Methods of Assessing Patients after Treatment

Diseases differ greatly in method of assessing the post-treatment condition. Even a disease like cancer presents problems (Dorn, 1951; Hopkins, 1953; Lees and Lees, 1950; Park and Lees, 1951), and the difficulties in rheumatoid arthritis, already referred to, are in many respects greater. The American Rheumatism Association scheme (Steinbrocker and others, 1949) promotes a standardization and objectivity that were much needed (Steinbrocker, 1946), but it still allows too great opportunity for inter-observer differences, and it is undergoing revision.

There may be surprisingly large differences between clinicians' findings in commonplace observations, such as interrogation of persons regarding the history of dyspepsia, presence of cough, and occurrence of sputum (Cochrane and others, 1951; Fletcher, 1951). In chest-film assessments, inter- and intra-observer variations have been studied extensively (Birkelo and others, 1947; Fletcher, 1951; Garland, 1950), but less attention has been paid to other regions.

If, for example, a radiologist is assessing films of rheumatoid joints, what effect has his knowledge of the treatment (cortisone or not cortisone), and the temporal sequence of the films?

It might be replied that the particular radiologist has no stake in the effects of cortisone one way or the other, and that films out of order would cause mental confusion. This answer would hardly satisfy anyone who, starting with a perfectly open mind, has felt bias creeping on him in a series of histological assessments. In any inspectional assessment, even the effort to avoid bias can create bias, and blindfold assessment is the only safeguard. Strictly random order, where possible (*e.g.* in a set of films or slides), controls also the bias due to a "drift" or "trend" in the observer, which is commoner, even in measurements, than medical observers apparently realize.*

Blindfold clinical assessment is possible to only a very limited degree (*e.g.* by arrangement with colleagues who are ignorant of the treatment). Hence the value of such devices as rings to measure the swelling of finger joints.

Methods of Collecting Data

Case Records.—Hospital records are known to contain undependable clinical data and grossly misleading laboratory reports (Belk and Sunderman, 1947), but chiefs of service are perhaps less aware than their juniors of the risk of purely fictitious

* Randomization methods suitable to this and other problems are described by Mainland (1952, p. 267), but the method shown there for allocating two treatments to equal numbers of subjects can introduce bias, as can coin tossing. For a simple unbiased method see Herrera (1955).

entries (Mainland, 1952, p. 240). These errors may, indeed, not affect a patient's welfare greatly, for a clinician who knows his patient well needs few notes. Most disconcerting, however, is the fact that, although they know how undependable individual records may be, many clinicians are very ready to draw conclusions from a table of percentages derived from a mass of such records. However large the mass, systematic errors (all in the same direction) do not "average out", and large random errors (of the $\pm$ type) cause serious lack of precision.

Clinical training and the pressure of routine work do not make for reliable record keeping, and experience in making clinical records, as well as in trying to use them, has led the author to believe that the only records trustworthy for research are:

(1) those kept meticulously by a physician regarding his own patients because he wishes to do so,
(2) those kept regarding a particular group of patients by a suitable and adequately instructed person, specially assigned to the task.

Patterson (1954) rightly regrets the appearance of a tendency to place "too much emphasis on the prospect of research work being made possible by elaborate systems of record keeping which would enable clinicians to get all sorts of statistical material on request". As he says, "the fundamental duty of the records officer is to produce the record when it is wanted, the whole record, and at once".

Planning of Record Forms.—If records are desired for anything more than their primary purpose (help in treating the patient), thorough planning is necessary. In such planning the *first* two requirements should *not* be: How can we avoid omitting data that may be wanted in some future research? and How should the inquiries be formulated for transference to punch cards?

A proposed routine record scheme for skin cancer patients covered four types of study:

(1) aetiological, *e.g.* family history of tumours, parents' eye colour, patient's exposure to light;
(2) therapeutic, *e.g.* cure rate, relation to dosage, five-year follow-up;
(3) socio-psychological and economic, *i.e.* reasons for delay in obtaining treatment;
(4) anatomico-pathological, *i.e.* location of various types of tumour.

Adequate exploration of all these topics would require a vast multitude of questions. For example, the question on the family history of tumours, showing four possible answers (Yes, No, Questionable, Name of Organ) should be either deleted or expanded until it created a family tree.

Regarding punch cards, it should be remembered that questions on any subject, real or imaginary, *can* be adapted to a card-sorting machine, and that it is not the function of a tabulating or business machine company to guard its customers against wrong questions or false data.

Hill (1951a) has declared that, in planning a questionnaire, for every question that a planner proposes to ask a respondent, he should ask himself at least three questions. A similar rule in the planning of a record sheet produces three sets of preliminary questions (on topics, on responses, and on the use of the answers), with three questions in each set.

Questions on Topics for Survey

(1) What information do we desire soon?
10 years hence, a skin cancer patient's excretion of some urinary constituent, now unknown, may be of far greater interest than his family tree.
(2) Of the topics that interest us, which can be profitably studied from routine case records?
The most suitable topics are frequencies or averages, such as proportions of different diagnoses made in one clinic in a year; relative frequency of skin tumours in different parts of the body; percentage of patients with a certain disease improved after 12 months' treatment. (For other types of question, see *Causal Relationships*.)
(3) Among the topics amenable to case record study, what difficulties were met in the best work already done, and how far can we overcome them with our facilities?

Questions on Responses.—The proposer of any question for the record sheet should ask himself:

(1) What are all the possible answers to this question, and are they shown alongside the question?

The Cortisone Study sheets (Figure, p. 327) purposely did not indicate all possible answers. Under "Subcutaneous Nodules", for instance, they omitted the possibility that new nodules might appear, and that some nodules might enlarge while others diminished. In a final survey this would not be allowable, for it might lead to bias in various ways.

For example, one careful observer omitted statements on nodules regarding patients in whom, as subsequent inquiry revealed, some nodules had enlarged and others had decreased. Other observers, doubtless in the same predicament, had presumably chosen one or other of the printed answers, and the grounds of choice could not be ascertained.

Answers headed "Other" and instructions to "Amplify on reverse side" conduce greatly to bias, because responses vary from nothing to abundant detail. They are valuable, however, for anecdotal purposes and in a preliminary exploration to reveal the quality and difficulties of respondents.

(2) What are the various possible interpretations of the question by the person who has to answer it—patient, physician, technician, or other respondent?

In some instances no uniform interpretation is possible. For example, in 51 per cent. of the first 446 data sheets received in the Cortisone Study the "Year of Onset of Disease" was stated to be the same as the "Year of Onset of This Attack", sometimes many years before the start of the therapy under investigation. The distinction seems to be inapplicable in rheumatoid arthritis.

(3) What factors, other than misinterpretation of the question, may cause the answer to be untrue, or elicit the response "Don't know"? Besides gross errors in records, already mentioned, the following three factors should be considered:

(*a*) Lack of remembrance or of knowledge (which may be registered as a biased guess).

Patients' power to recall events and dates is much less than many physicians seem to believe, and independent checks are seldom possible. Some questions a conscientious respondent would find very difficult; for example, in a rehabilitation follow-up questionnaire: "How many hours a day do you stand?"

(*b*) Ulterior motives, such as hope of gain or desire to please.

Even the final verdicts on the outcome of treatment, on case records, or on certificates from certain sources, are greatly influenced by various motives. Therefore anyone, including an unsuspecting statistician, who plans to use data from large organizations, governmental or other, should, indirectly and discreetly, acquire an insight into the factors that may have been operating when the statements were made. (This would save some expensive retrospective and follow-up studies.)

(*c*) Emotional factors.

When fearful of a particular diagnosis or bewildered when it is made, no patient should be expected to answer objectively. Even in healthy people the questionnaires themselves may produce symptoms (*British Medical Journal*, 1954; Glaser, 1954)—apart from the anger which would be the most appropriate response to some lists of questions.

At an early stage, proposers of questions should test them on colleagues, non-medical acquaintances, and patients, including the less intelligent and less co-operative. Because of the unreliability of patient response, no conclusions were drawn from such information in the Cortisone Study.

Questions on the Use of Answers.—Visualizing the use of each answer, the proposer should ask:

(1) In what ways may the user interpret the answer? Will he know what it really means?

(2) If answers to some of the questions are to be combined, how is this to be done, and what will the composite answer tell one? For example, if an index of capacity for activities of daily life changes or remains the same in an individual, what inferences can be drawn?

(3) Exactly how is the answer to be used?—see skeleton Tables discussed under *Purposes of the Survey*. The proposer should prepare such Tables even if he does not expect to use the answers himself, for then he will be forced to ask what must be done with doubtful or ambiguous answers, blanks, and descriptive answers.

Mail Questionnaires.—The foregoing recommendations apply also to mail questionnaires, but here the questions should be very few. Hill (1951a, 1951c, 1953) half-facetiously suggested a maximum of five, but showed how, without exceeding that number per person, answers to more than five questions could be obtained.

Extracting Information from Records

When record sheets are properly planned for a particular survey and data are properly entered, extraction from the records consists essentially in copying. The Cortisone Study illustrated a much commoner set of circumstances. The interest in cortisone had resulted in more detailed case records than are usual in many diseases, but many of the questions asked in the Study were not directly answered by the original records.

Preliminary Study.—In such circumstances the preliminary study should follow the lines recommended for the planning of record sheets, but should also explore specimen records fully, especially the more difficult ones, and from all clinics if a co-operative study is projected, the purpose being:

(1) to test the proposed questions,
(2) to consider the usefulness of the data (apparent reliability, ambiguities, blanks),
(3) to formulate instructions for transcribers.

Instructions should take nothing for granted. The Cortisone Study revealed that in a pilot or final study they should state: the equivalence of ACTH and corticotrophin, trade names for gold preparations, the distinction between intercurrent and concomitant therapy, and the intention to include oral hydrocortisone (oral compound F) in the survey.

The analyst in a survey, whether clinician or statistician, should never need to seek interpretation of an answer in one section by referring to another section, perhaps to a third, and then to remarks volunteered on the reverse side.

Members of the Cortisone Study planning committee remarked that if many instructions were sent, the transcribers would not read them, and even the few instructions that were issued were often ignored. The analyst had to make many calls for elucidation, and her fear of undetectable errors grew ever stronger. If a clinic has

no transcriber with the ability, time, and willingness to follow necessary instructions minutely, its contribution to a survey will be useless.

If, however, more than a few instructions for the *interpretation* of the record sheet data are found necessary, this should raise the fear of bias through arbitrary interpretation of records that are unsuitable for anything except an anecdotal survey.

Risks of Interpretation.—The dangers attendant on using records not designed for the particular survey were present in two areas of the Cortisone Study that would have been vital in a final survey. The transcribers, not necessarily acquainted with the patients, were required:

(1) to translate recorded data into the Stage, Class, and Grade of the American Rheumatism Association scheme,

(2) to state the reason for permanent cessation of cortisone treatment, which might often entail an inference, not merely a transcription, from the original records.

Extensive checks would have been necessary to show the full effects, but it was noted that out of 28 patients whose cortisone was stated to have been stopped because of remission, eight were stated to have shown a Grade II improvement, whereas by definition Grade I = remission.

When trying to infer the reason for stopping cortisone, the transcriber would find in the records evidence that the patient was not doing well, or evidence of toxicity, or both. If both, he would not necessarily give to each factor the weight given by the physician who had stopped the drug; and other factors, such as financial circumstances, might not be recorded at all. Discrepancies between answers regarding the same patient reflected the difficulty.

When a physician has extracted and interpreted the information from his own records of private patients, the accuracy of interpretation will be greater, but even then the question could be asked: "Would he have given the same verdict (Class and Grade) for the 6-months observation if he had not known what was to happen later?" One cannot be certain, either, that he would in all cases recall the degree of importance that he had given to the various factors when stopping cortisone. Indeed, even at the time of stopping it he would have found the weighting difficult in some patients.

It seems doubtful, therefore, if even a perfect survey could give a simple answer to such a question as: "In patients whose cortisone was not stopped because of toxicity, what was the condition at 12 months?"

A more reliable statement would be obtained by pooling data from all patients whose cortisone had been stopped because of toxicity, inadequate benefit, or both.

Pilot Study.—If a preliminary study does not show that the survey should be dropped or made purely anecdotal, a pilot study may be started, preferably on random samples of the records, in order to provide estimates of sample size required in the final study. The general technique is not difficult (Mainland, 1952, p. 271), but in applying it the help of a statistician well versed in sampling is usually desirable. To take every second, fifth, or tenth record is likely to give a false estimate of variability.

In any pilot or final survey, numerous cross-checks between transcribers are necessary to avoid serious differences in interpretations (Densen and others, 1952).

Time Factors

> Essentially all the problems of chronic disease epidemiology revolve around the time factor, since every characteristic by which a group of people is commonly classified, except their sex and race, can change with time. (Sartwell and Merrell, 1952).

An investigator of a chronic disease should, during the planning, analysis, and presentation of results, ask such questions as:

(1) Will this estimate (*e.g.* percentage of patients improved, average erythrocyte sedimentation rate, incidence of toxicity) apply equally to adults and children, young adults, the middle-aged, and the aged? If not, is the difference important in our use of the estimate?

(2) Is it safe to pool several years' experience of this therapy? (Types of patient selected, dosage schemes, and the initial optimism regarding a drug can change greatly in the first 5 years after its introduction.)

(3) What allowances should be made for the duration of treatment, observation, and exposure to risk (of disease, recurrence, or toxicity)?

In the preliminary report on the Cortisone Study (American Rheumatism Association, Panel Discussion, 1953), in order to give at short notice a picture of the material collected, some percentages from the pooled data were presented without any allowance for the time factor, and the subsequent general discussion, with audience participation, showed that this was a mistake.

Estimates from such pooled data, even from a single clinic, would be applicable only to a population that had the same composition, in duration of treatment and observation, as the group studied—so many patients treated for 12 months, so many for 13 months, and so on. The patients actually studied would be a different population a month later. To obtain an estimate with useful meaning, one must show what has happened to the patients at some fixed time after starting treatment—the time being the same for all patients. (Comparison of patients treated in the early part of the survey

period with those treated later will be discussed in the article on analysis.)

Another effect of the time factor was pointed out by Kellgren (1953) in the discussion of the preliminary report of the Cortisone Study. In a disease characterized by remissions and exacerbations, treatment does not begin in remission. Therefore, even if a therapy has no effect at all, at any given point in time after it has started, some of the patients should be expected to be in remission.

Numbers of Patients and of Observations

A primary question in any investigation is: "Have we enough material to provide useful estimates?"

In a clinical record survey the answer involves:

(1) Losses from the sample;
(2) Fictitious sample sizes;
(3) Sample size and confidence limits.

(1) Losses from the Sample.—These include disappearance of patients, interruptions of treatment, losses of records, blanks in records, and failures to come for examination or to answer questionnaires. If the losses were strictly random they would merely reduce precision; but the only safe assumption, usually, is that the losses are not random.

Patients whose treatment has been stopped because of remission tend to disappear, and so do patients discouraged by lack of benefit. Blanks in records may indicate mere accidental failure to record a test or treatment, or a belief that such a test or treatment was unimportant, or lack of interest in the patient, which itself can affect the outcome. Specially "interesting" case records or *x*-ray films, removed from the series for study or teaching, may also be lost.

In a mining population of 600, all of whom were voluntarily *x* rayed, those with pneumoconiosis mostly came up first, and those with tuberculosis came last (Cochrane in discussion of a report by Stewart, 1951). Lack of insistence on a full survey would have caused bias.

In questionnaires it should be assumed that non-respondents' answers would differ, to a greater or less extent, from the answers received, unless this can be disproved experimentally—a difficult task, for it involves measures to insure that answers are received from a strictly random, and sufficiently large, sample of the non-respondents. It was this danger of bias that led Hill (1951a) to declare:

> I would therefore myself infinitely sooner have, say, a one in four [random] sample of the population, of a size thereby which enabled me to pursue relentlessly, and complete the records for, all or nearly all the persons in it, than have to interpret figures derived from survey of the "whole" population from which finally a quarter was missing.

Treatment of Losses.—Occasionally, blanks in the records can be safely filled in by interpolation, and very occasionally, after much critical thinking, by extrapolation.

Where losses in a therapeutic survey are due to death, accident, intercurrent disease, or change of residence, these patients can be excluded from the population, provided that the events are entirely independent of the disease and therapy. In rheumatoid arthritis pregnancy should also exclude patients, because in many women it has a beneficial effect.

In reporting a survey, three basic rules should be:

(1) State how any exclusions modify the definition of the population.
(2) Account for all losses, at whatever stage they occurred.
(3) Show the effects of the various possible allocation of losses, as exemplified in the following paragraph.

Tolerance Limits.—The tolerance limit of about 5 per cent. (Doll, 1951) for loss in questionnaires (except when purely anecdotal) is applicable to other surveys. Investigators should, however, see for themselves in the preliminary study what the amount and effects of losses and blanks may be. Thus, fifty records in a certain group (*e.g.* females over age 40, initial condition: Stage II), classified according to condition (A or B) after 12 months' treatment, might show:

A: 10. B: 35. Losses or Blanks: 5.

The possible estimates are:

From available information on 45 patients.—
A: 22 per cent.; B: 78 per cent.
If losses or blanks were As.—
A: 30 per cent.; B: 70 per cent.
If losses or blanks were Bs.—
A: 20 per cent.; B: 80 per cent.

If, instead of A and B, the estimates were average measurements (*e.g.* E.S.R.) the two suppositions would be:

(1) that all losses or blanks contained low readings,
(2) that all losses or blanks contained high readings.

Obviously, losses of fewer than 5 per cent. of the total patients in a survey may render useless the data in some sparsely peopled categories.

(2) Fictitious Sample Sizes.—Samples can be rendered fictitiously large in several ways, such as:

(1) inclusion of supplementary cases,

(2) spurious replication,
(3) pooling of heterogeneous data, as in co-operative surveys.

Supplementary Cases.—Except for anecdotal purposes, it is seldom useful, always troublesome, and often misleading, to include a few subjects outside the main class under study. Five children would have to differ from adults enormously in response to treatment before they could differ "significantly" in the statistical sense, but to apply to children the estimates from adults (or from adults plus children) could be grossly misleading.

Spurious Replication.—In a study of anaesthetics in children it was proposed to use 343 administrations as denominator in estimating the percentage frequencies of various reactions, but only 148 children had been observed (one to fourteen administrations per child). The only safe assumptions, however, were that:

(1) a child would often tend to react in a similar way to the same anaesthetic on different occasions,
(2) a first administration might influence the reaction to later ones.

The "sampling unit" should have been the first administration in each child (although further study of multiple administrations could, of course, be made). Spurious replication ("counting the same thing over again") is not uncommon (Mainland, 1952, p. 32; Mainland and Herrera, 1954b).

Heterogeneous Data in Co-operative Surveys.—The main reason for a co-operative survey is to increase sample size. Such a survey usually requires expert help in planning and analysis; but as soon as it is thought of, one general outcome should be anticipated. If, after it is completed, averages from pooled data are presented, some of the investigators will accept them, but others will probably dispute them because the estimates do not agree with their own experience, and this is the safer attitude.

Even if the survey were perfect in all respects, and if groups of patients, one group from each clinic, could be matched according to all the categories in the records (sex, age, initial severity, chief and concomitant therapy, and other relevant features), there would still remain unrecorded but relevant inter-clinic differences in the environment and personalities of patients, diagnostic methods, therapy, and judgment and personality of physicians and other attendants. Major factors would be the physicians' differences in the selection of patients, on the basis of history, for the therapy under study, and their interpretation of standard criteria of status and progress.

Therefore, 222 rheumatoid arthritics from 23 clinics, in Stage III at the start of therapy, are not to be considered as a single sample but as 23 samples, each from a different population. The estimates (*e.g.* percentage improved or toxic after 12 months' treatment) will perhaps not differ between clinics more than is often attributed to chance, *i.e.* they may not be significantly different at the 5 per cent. level, and that will be discussed in the article on analysis, but it is generally safest to assume that the observed differences represent actual differences (heterogeneity).

Hence, even without further division into sub-populations, the above figures would provide 23 estimates with differing sample sizes, and the pooling of the data could take one of two forms:

(1) *A Weighted Estimate.*—If fifty of the total 222 patients showed improvement, the weighted estimate would be $50 \times 100/222 = 22{\cdot}5$ per cent. This gives greatest weight to the clinics that contributed most patients, but the size ratio of the 23 samples does not represent anything general, such as a nation-wide ratio of clinic population types. The percentage represents an estimate of the value that would be approached if one could take larger and larger samples of the same types of patients from the same clinics and in the same ratio of sample sizes—not a very helpful piece of information.

(2) *An Unweighted Estimate.*—This would be obtained by finding for each clinic the percentage improved, totalling the 23 percentages, and dividing by 23. It is an estimate of the percentage that would be approached if one could obtain larger and larger samples, all equal in size, from the same clinics, and pool them (or, of course, find the average of their percentages).

> If it could be assumed that the 23 clinics formed a random sample of a population composed of all rheumatic disease clinics (each clinic being a unit), the unweighted average would be an estimate of the average for this population. During the period covered by the Study, the 29 clinics that furnished data probably comprised the majority of the clinics in North America, but the 29 were not a strictly random sample; and still less were they a random sample of the much larger number of clinics now in existence.

The safest and most reliable treatment is to use with each clinic its own estimate. This seems to throw doubt on the usefulness of co-operative studies; but with reliable data they could be very useful, for they would enable one to compare, contrast and perhaps combine information, obtained from the data of each clinic separately, on trends of improvement or retrogression of patients.

> Elaborate methods were not justified in the Cortisone Study, and unweighted averages, without estimates of error, were used in order to give a rough picture of the change in patients' status during the 2 years.

(3) **Sample Size and Confidence Limits.**—Even with no losses or blanks, a sample may be too small to give a useful estimate, because possible variation due to chance must always be allowed for. Thus, if of fifty adult female cortisone-treated arthritics, after 12 months' treatment, fifteen (30 per cent.) showed improvement and 35 (70 per cent.) showed retrogression or no improvement, the true (population) percentage of improved cases in the same type of patients, treated in the same way, might lie anywhere between 18 and 45 per cent., but would probably not lie outside this range. If an investigator uses these estimated limits, and corresponding estimates in other problems, he will be correct in 95 per cent. of such judgments regarding the effects of chance. That is, he has a 95 per cent. probability of being correct in any one judgment, and the limits are called "95 per cent. confidence limits".

Such estimates of error are necessary in all scientific work on either frequencies or measurements, but they are often omitted in medical research (Mainland, 1954c). For percentage frequencies in two-class (binomial) samples (*e.g.* improved, not improved) the limits can be easily found from Tables and Graphs (Mainland, 1952, pp. 53 and 311), and more detailed Tables are in preparation (Mainland, Herrera, and Sutcliffe). The commonly used approximation, derived from the standard error of the binomial, can be misleading in many samples met in clinical research.

Causal Relationships

Even a perfect survey could demonstrate only an *association* between phenomena, not a causal relationship, which a properly conducted experiment could prove with a specified probability. Sometimes the survey method has led to correct causal inferences of great practical value, the most famous example probably being Snow's tracing of a cholera epidemic to the Broad Street pump in London (Hill, 1953); but such successes are to be expected only if a survey approaches an experiment in design and execution, particularly with reference to controls (perhaps better called "contrasting samples") and to selection of samples. These two features can be considered in relation to four kinds of topic on which information is often desired from case records:

(1) Aetiological relationships or clues thereto, such as sex incidence, age incidence, and relationships to other diseases;
(2) Comparative therapeutic effects of different dosage schemes;
(3) Relationship between dosage and toxic effects;
(4) Interrelationship of phenomena within a disease (discussed later, under *Fallacy due to Competing Selection Rates*).

(1) Aetiological Relationships

Lack of suitable controls is the chief reason why case record surveys are seldom of use in studying the relationships of diseases to other phenomena, events, or attributes, including other diseases—for example, the relationship of skin cancer to eye colour, myocarditis to rheumatoid arthritis, and peptic ulcer to personality. It is hazardous to employ as controls patients with all other diseases or certain selected diseases in clinic or autopsy records. Even the most careful choice of controls does not eliminate the risk of a subtle bias (discussed under *Fallacy due to Competing Selection Rates*).

Much more easily avoided, but still frequently committed in medical writing, are blunders due to ambiguity in terms like "sex incidence" and "age incidence". It would, presumably, be unreasonable to doubt that rheumatoid arthritis, sufficiently severe to bring patients to physicians, is more frequent in women than in men; but figures such as 60 per cent. women and 40 per cent. men, *obtained from rheumatoid arthritic patients*, do not, by themselves, justify the inference at all. Underlying the inference are two assumptions:

(1) The existence of a control or standard of comparison—roughly equal numbers of men and women in the total population,
(2) The absence of selection factors, such as have affected dermatologists' records of the sex ratio in acne—the tendency of girls to be more concerned than boys about their appearance (Sulzberger, 1955).

As commonly used, "incidence" is equivalent to "percentage frequency" (or frequency per thousand, per hundred thousand, and so on), without reference to the epidemiologist's distinction between "incidence" and "prevalence". The figures 60 and 40 per cent. show the incidence of women and the incidence of men in a group of arthritics, not the incidence of arthritis in women or in men.

To obtain, for any particular place and time, the incidence (the epidemiologist's "prevalence") of a certain disease in women there would be needed, for the numerator, the number of women who had that disease (say, A). For the denominator there would be needed the same women (A) plus all the other women (B) who would have appeared in the numerator if they had had the disease; and likewise for the incidence in men.

The denominator (A + B) is the "population at risk", or, as sounds more appropriate in non-infectious diseases, the "source population"; and the source populations for case records are unknown, except in special groups such as the armed forces and some industrial companies.

The denominator used in the estimates, 60 per cent. women and 40 per cent. men, was the total

number of arthritics; this fault of "wrong denominator" has led to many invalid conclusions, such as an association between amenorrhoea and sedentary work (Mainland, 1952, p. 33), and is very commonly found in relation to "age incidence".

somewhat fewer women who have not previously developed it).

In the left part of the Figure the slope might have been vastly different if, instead of concentrating on rheumatologists, the Cortisone Study had included paediatricians and general practitioners.

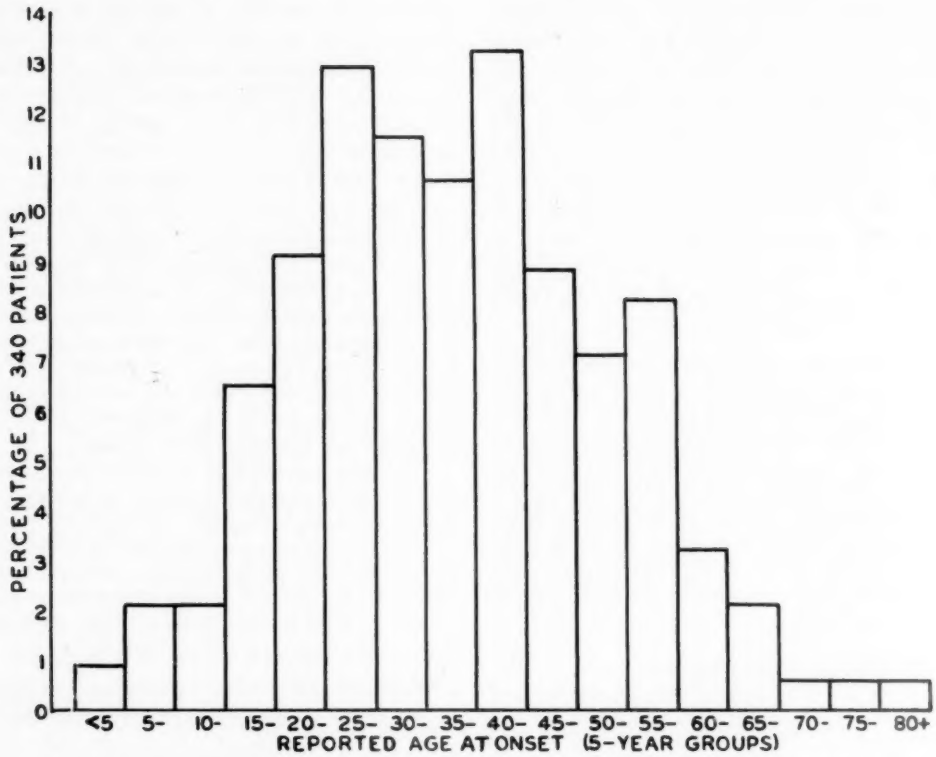


Figure.—Frequency distribution of ages at onset of rheumatoid arthritis reported in 340 female patients.

The Figure shows the frequency of the ages at onset of rheumatoid arthritis in 340 females (as reported in the Cortisone Study and used here for illustration only). The percentages were found by dividing the number of female patients in each age group by the total number of female patients, but the shape of the graph would be the same if the actual numbers had been used. It shows incidence of ages in arthritics, not incidence of arthritis in different age groups of women. For the latter, the proper denominators would be the source populations (females in each group)—again unknown denominators.

Such graphs would not mislead if they were given a little thought. Thus, if the percentage frequency of onset of arthritis were exactly the same in all age groups and if all arthritics were seen, the right part of the graph should, nevertheless, be expected to slope down, simply because there are progressively fewer women alive to develop the disease (and also

The dip in the central part of the Figure, however suggestive, and even if "statistically significant", tells nothing in the absence of the source populations.

The error of "wrong denominator" is committed twice over in such comparisons as the "age incidence" of gastric and duodenal ulcer criticized by Hogben (1945), where peaks occurred at different ages. It was quite unsafe to assume that the source populations and sample selection factors were the same for the two groups.

(2) Comparison of Dosage Schemes.—The amount and scheduling of a therapy are nearly always determined largely by the apparent needs of the patient throughout the treatment. Therefore the comparison of effects of different doses or schedules is argument in a circle—a fact that seems to need frequent reiteration (Hill, 1952).

The circle is less obvious, but still usually present,

in demonstrations of relationships between dosage and phenomena that were not used by the physician as indicators for dosage change. In rheumatoid arthritis such phenomena might be bone density or results of C-reactive protein tests. Unless the phenomena can be shown clearly to have no relationship to the dosage indicators, the demonstrations are fallacious.

(3) **Dosage to Minimize Toxic Effects.**—Although by no means comparable to an experiment, a survey of case records might give some useful information on dosage-toxicity relationships if the investigator could overcome certain difficulties, chiefly of definition:

(1) Definition of toxicity (side-effects).

(2) Period of observation—the same for all patients.

(3) Definition of dosage—size of each dose, intervals, total for a period.

In the Cortisone Study the doses were divided into less than, and more than, 50 mg. daily; but the lower dose is quite inadequately defined, for this class would include patients on very small and infrequent doses. The almost infinite variety of dosage procedure seen in the Cortisone Study illustrates the great difficulty of finding a satisfactory dividing line between "low" and "high" doses, even in an individual clinic.

(4) Exclusion of possible causes other than the treatment. To avoid difficulty and prejudice, it is probably best to count as actual or possible side-effects all events (of predefined types) that could have been due to the treatment.

(5) Pooling of all patients or division by severity of disease, concomitant therapy, and other relevant features. Subclasses may be too small for the necessary precision, but the whole group of patients may be too heterogeneous for useful estimates.

The conclusion of many attempts to establish a dose-toxicity relationship must be simply the obvious one that, usually, the less of a drug is given the lower is the risk of toxicity.

Fallacy due to Competing Selection Rates (Berkson's Fallacy)

At one time surgeons were prompted to remove the gall bladders from diabetic patients because of an unusually high frequency of cholecystitis in diabetics, and this inference seemed to be confirmed by using, as a control sample, persons who came to a clinic for eye testing. Berkson (1946) showed, however, that such an association, demonstrated by comparing in hospital patients the incidence of a Disease X in samples of two other diseases, A and B, can be entirely spurious, in the sense that it does not reflect an actual association outside the hospital sample. It can be due solely to the fact that different diseases lead to different percentages of diseased persons admitted to hospital.

Mode of Operation.—The way in which the bias is created is easily demonstrated by simple arithmetic (Mainland, 1953; Mainland and Herrera, 1954a), and the outcome of one such demonstration (one mode of operation of the bias) can be described thus:

In the population outside the hospital the percentage frequency of persons with Disease X was exactly the same in persons with Disease A and with Disease B. Disease A had a higher admission rate than Disease B, and in the hospital samples there was a higher percentage frequency of Xs among the Bs than among the As. In such cases the higher rate in the As seems to push the Xs into the Bs; and, to extend the terminology beyond hospital examples, one can speak of "competition between selection rates". The difference in percentage frequencies, it should be noted, can be very large and highly significant in the statistical sense.

Scope.—Unless there is strictly random sampling from the population regarding which an inference is to be made, the bias, though unsuspected and often undetectable, can cause fallacious inferences from a survey of any phenomena by creating a spurious association, masking a real one, or reversing it. Thus it can throw doubt on inferences from autopsy records (Mainland, 1953), attempts to relate lung cancer and smoking (Berkson, 1955), studies of blood groups in disease, and physiological and anatomical surveys (Mainland, 1955). It can occur, of course, where more than two samples, and more than two classes of individuals, are analysed. It can affect measurements as well as frequencies, but this field has not been explored.

Effect on Relationship within a Disease.—The fallacy could vitiate any inferences regarding interrelationships of phenomena in a disease, either a status (when the patient is first seen) or a change in phenomena during therapy—for example (in rheumatoid arthritis), *x*-ray assessment, C-reactive protein, erythrocyte sedimentation rate, subcutaneous nodules, numbers of joints involved, functional activity, improvement, or resistance to therapy.

As a hypothetical example, let it be supposed that:

(1) There is no association between the presence of subcutaneous nodules (X) and resistance of the disease to therapy;

(2) Patients whose disease is more resistant to treatment (As) are more frequently referred to a certain specialist than are patients with less resistance (Bs);

(3) Patients with abundant nodules have a greater tendency to seek the specialist's help than those with few nodules or none.

The scheme described above, using the same letters (A, B, and X), shows that the specialist will find in his sample of arthritics a greater frequency of patients with nodules in the less resistant cases than in the more resistant cases.

By contrast, let it now be supposed that patients with subcutaneous nodules are, in fact, commoner among those who are resistant to therapy. It can be shown, again by simple arithmetic, that this factor can neutralize competition between selection rates, so that the specialist will find approximately equal percentage frequencies of nodule-bearing subjects among the more resistant and less resistant patients. Or, if the association between nodules and resistance is very strong, he will find evidence of it in his patients, but diluted by the competition between selection rates.

Suggestions for Counteracting the Fallacy.—The implications of Berkson's fallacy raise the question: "Have non-experimental observations on patients any more than anecdotal value?" For clinical purposes they certainly have, when properly made. If in a certain clinic an association has been found between a feature, present in patients before treatment, and their improvement or lack of improvement under treatment, that association will be useful in prediction and as a guide to therapy, even although it has arisen through competition of selection factors —providing, of course, that the factors remain stable.

Regarding deeper exploration of relationships between and within diseases, suggestions such as the following can, so far, only be general:

(1) Investigators, including experimenters and practical statisticians, should explore the various ways in which the bias can occur, using simple arithmetical examples at first, until they come to think of it automatically in any problem.

(2) In each particular problem they should try to think of all possible ways in which the bias might occur, and see whether at least some of the possibilities cannot be excluded. For example, if a scheme involved the assumption that in a specialist's practice mild cases were more frequent than severe cases, the scheme could usually be ruled out. (Even this example partly breaks down when a specialist treats many mild cases among his medical colleagues.)

(3) When a survey has revealed an association between phenomena (or lack of an association that was rationally anticipated), repetition of exactly the same kind of exploration in other places, though useful, is not enough, because the same selection factors may be at work. Where possible, it is better to explore, in circumstances where the selection factors are likely to be different, other aspects of the relationship under investigation. Here and there it may be possible to reinforce survey by experimentation, and ultimately considerable confidence, psychological rather than numerical, may be felt in the interlocking evidence. The process is, in fact, a miniature replica of the one by which some of the major biological theories have been established.

Summary

With the aid of examples taken chiefly from the American Rheumatism Association's Co-operative Study of Cortisone in Rheumatoid Arthritis, the possible usefulness of surveys of case records is examined.

A controlled trial would be necessary to measure the benefit actually due to a treatment, but a properly conducted survey can assess improvement after treatment, provided that the records are suitable and lost cases are few. Because therapy in most chronic diseases is multiple, the assessment must often refer to all patients with a certain disease in a certain clinic or subgroup, rather than to patients treated by any one method.

Aetiology and the relationships, or differences, between diseases can seldom be satisfactorily studied from case records.

Unless a survey is very carefully planned and executed, it can have "anecdotal" value only.

Satisfactory co-operative studies are very difficult, and, even if a perfect survey were possible, interclinic differences in verdicts should be expected.

Detailed recommendations are made regarding the planning of case-record surveys and follow-up studies.

Common errors are discussed, such as the misinterpretation of "incidence", and the belief that dosage-response relationships can be measured even though doses are changed at will during treatment (a circular argument).

Any inference from a survey, such as an association (or lack of association) between phenomena in two diseases, or within a single disease, can be fallacious because of undetected bias due to competition between selection rates (Berkson's fallacy). Some general methods are suggested for partial counteraction of this bias.

I am greatly indebted to Miss Claire Lingg for many of the examples quoted from the Cortisone Study as well as for valuable comments, to Mrs. Lee Herrera for meticulous and constructive criticism throughout the preparation of the article, and to members of the Cortisone Study Committee—Drs William H. Kammerer, Currier McEwen, Charles Ragan and Morris Ziff—for their careful scrutiny of the manuscript and for very helpful suggestions.

REFERENCES

American Public Health Association. Committee on Sampling Techniques (1954). *Amer. J. publ. Hlth*, **44**, 719.
American Rheumatism Association (1953). *Annals of the Rheumatic Diseases*, **12**, 329.
—— (1955). *Ibid.*, **14**, 325.
Asher, R. (1954). *Brit. med. J.*, **2**, 460.
Belk, W. P., and Sunderman, F. W. (1947). *Amer. J. clin. Path.*, **17**, 853.
Berkson, J. (1946). *Biometrics Bull.*, **2**, 47.
—— (1955). *Proc. Mayo Clin.*, **30**, 319.
Birkelo, C. C., Chamberlain, W. E., Phelps, P. S., Schools, P. E., Zacks, D., and Yerushalmy, J. (1947). *J. Amer. med. Ass.*, **133**, 359.
British Medical Journal (1954). **1**, 1366.
Cochran, W. G. (1951). *Amer. J. publ. Hlth*, **41**, 647.
—— (1953). *Ibid.*, **43**, 684.
Cochrane, A. L., Chapman, P. J., and Oldham, P. D. (1951). *Lancet*, **1**, 1007.
Cornfield, J. (1951). *Amer. J. publ. Hlth*, **41**, 654.
Daniels, M. (1951). *Brit. med. Bull.*, **7**, 320.
Densen, P. M., Padget, P., Webster, B., Nicol, C. S., and Rich, C. (1952). *Amer. J. Syph.*, **36**, 64.
Doll, R. (1951). *In* "The Application of Scientific Methods to Industrial and Service Medicine": Proceedings of a Conference held March, 1950, p. 16. Medical Research Council, H.M.S.O., London.
Dorn, H. F. (1951). *Brit. J. Radiol.*, **24**, 295.
—— (1953). *Amer. J. publ. Hlth*, **43**, 677.
Fletcher, C. M. (1951). *In* "The Application of Scientific Methods to Industrial and Service Medicine", p. 87. H.M.S.O., London.
Garland, L. H. (1950). *Amer. J. Roentgenol.*, **64**, 32.
Glaser, E. M. (1954). *Clin. Sci.*, **13**, 475.
Green, F. H. K. (1954). *Lancet*, **2**, 1085.
Greenberg, B. G. (1953). *Amer. J. publ. Hlth*, **43**, 692.
Hansen, M. H., and Hurwitz, W. N. (1951). *Ibid.*, **41**, 662.
Herdan, G. (1955). "Statistics of Therapeutic Trials." Elsevier, Amsterdam.
Herrera, L. (1955). *Science*, **122**, 828.
Hill, A. Bradford (1951a). *In* "The Application of Scientific Methods to Industrial and Service Medicine," p. 7. H.M.S.O., London.
—— (1951b). *Brit. med. Bull.*, **7**, 278.
—— (1951c). *J. roy. statist. Soc.*, Ser. A, **114**, 1.
—— (1952). *New Engl. J. Med.*, **247**, 113.
—— (1953). *Ibid.*, **248**, 995.
Hogben, L. (1945). *Brit. med. J.*, **1**, 884.
Hopkins, C. E. (1953). *West. J. Surg.*, **61**, 149.
Kellgren, J. H. (1953). *Annals of the Rheumatic Diseases*, **12**, 337.
Lees, J. C., and Lees, T. W. (1950). *Cancer*, **3**, 377.
Mainland, D. (1952). "Elementary Medical Statistics. The Principles of Quantitative Medicine." Saunders, Philadelphia.
—— (1953). *Amer. Heart J.*, **45**, 644.
—— (1954a). *Meth. med. Res.*, **6**, 121.
—— (1954b). *Ibid.*, **6**, 152.
—— (1954c). *Ibid.*, **6**, 191.
—— (1955). *Ann. N.Y. Acad. Sci.*, **63**, 474.
——, and Herrera, L. (1954a). *Meth. med. Res.*, **6**, 159.
——, —— (1954b). *Ibid.*, **6**, 184.
——, ——, and Sutcliffe, M. I. (1955). "Statistical Tables for Use with Binomial Samples in Medicine and Biology." Department of Medical Statistics, New York University.
Ogilvie, H. (1949). *Brit. med. J.*, **2**, 663.
Patterson, W. G. (1954). *Ibid.*, **2**, 140.
Park, W. W., and Lees, J. C. (1951). *Surg. Gynec. Obstet.*, **93**, 129.
Ragan, C. (1955). Personal communication.
Sartwell, P. E., and Merrell, M. (1952). *Amer. J. publ. Hlth*, **42**, 579.
Steinbrocker, O. (1946). *J. Amer. med. Ass.*, **131**, 189.
——, Traeger, C. H., and Batterman, R. C. (1949). *Ibid.*, **140**, 659.
Sulzberger, M. (1955). Personal communication.
Stewart, A. (1951). *In* "The Application of Scientific Methods to Industrial and Service Medicine," p. 33. H.M.S.O., London.
White, C. (1953). *Brit. med. J.*, **2**, 1284.

L'emploi des dossiers des malades dans l'étude de la thérapie et d'autres traits d'une maladie chronique

I. Projet de l'enquête

RÉSUMÉ

A l'aide d'exemples venant surtout de l'Enquête en Collaboration de l'*American Rheumatism Association* sur la Cortisone dans l'Arthrite Rhumatismale, on examine l'utilité d'enquêtes employant des dossiers des malades.

Une expérience contrôlée serait nécessaire pour mesurer le bénéfice réel d'un traitement, mais une enquête bien dirigée peut évaluer l'amélioration après le traitement, pourvu que les dossiers s'y prêtent et que peu de cas se perdent. Comme la thérapie dans la plupart des maladies chroniques est multiple, l'évaluation devra toujours tenir compte de tous les malades atteints d'une certaine maladie dans une certaine clinique ou dans un groupe, plutôt que de malades traités par une méthode quelconque.

Les dossiers des malades ne se prêtent que rarement à l'étude satisfaisante de l'étiologie, des rapports ou des différences entre des maladies.

A moins que le projet et l'exécution d'une enquête soient très soigneux, sa valeur ne sera qu'anecdotique.

Des recherches satisfaisantes en collaboration sont très difficiles et même si une enquête parfaite serait possible, il faudrait s'attendre à des différences entre les verdicts intercliniques.

On fait des recommendations minutieuses concernant la manière de projeter les enquêtes utilisant des dossiers des malades et des données de la surveillance post-hospitalière.

On discute les erreurs habituelles, telles que l'interprétation erronée de la "fréquence" et la conviction que le rapport entre la posologie et la réaction thérapeutique peut être mesuré, même en changeant à volonté les doses au cours du traitement (un argument circulaire).

Toute déduction d'une enquête, telle que la présence, ou l'absence d'une association entre des manifestations dans deux maladies ou dans une seule maladie peut être fallacieuse en raison d'un parti pris (*bias*) méconnu dû à la concurrence entre les taux de sélection (sophisme de Berkson). On suggère quelques méthodes générales pour neutraliser partiellement ce parti pris.

Empleo de fichas de enfermos en el estudio de la terapia y de otros rasgos de una enfermedad crónica

I. Proyecto de una investigación

SUMARIO

Con la ayuda de ejemplos tomados principalmente de la Investigación Cooperativa de la *American Rheumatism Association* sobre la Cortisona en la Artritis Reumatoide, se examina aquí la utilidad posible de investigaciones que usan fichas de enfermos.

Se necesitaría un experimento controlado para medir el beneficio efectivo de un tratamiento, pero una investigación propiamente dirigida puede avaluar la mejoría después de un tratamiento, provisto que las fichas se presten a ello y que pocos casos se pierdan. Como la terapia en la mayoría de las enfermedades crónicas es multiple, la avaluación debe siempre tomar en cuenta todos los enfermos con enfermedad determinada y en una clínica o en un grupo determinado de preferencia á enfermos tratados con un método cualquiera.

Las fichas de enfermos permiten raramente un estudio satisfactorio de la etiología, de las relaciones o de las diferencias entre enfermedades.

A menos que el proyecto y la ejecución de una investigación sean muy cuidadosos, su valor no será más que anecdótico.

Un estudio cooperativo satisfactorio es cosa muy difícil y hasta con una investigación perfecta habría que anticipar diferencias interclínicas de dictamen.

Se hacen recomendaciones detalladas acerca de la manera de proyectar investigaciones con fichas de enfermos y de seguir la evolución posthospitalaria de éstos.

Se discuten los errores comunes, tales como la interpretación errónea de la "incidencia" y la creencia de que se puede medir la relacion entre las dosis y la respuesta terapéutica aunque se cambie libremente las dosis durante el tratamiento (un argumento circular).

Cualquier inferencia de una investigación, tal como afirmación o negación de la existencia de una asociación entre fenómenos en dos enfermedades o en la misma enfermedad puede ser delusoria a causa de un factor de parcialidad (*bias*) escondido, debido a la competición entre las razones de selección (sofismo de Berkson). Se sugieren algunos métodos generales para neutralizar en parte esta parcialidad.

Ann. rheum. Dis. (1955), **14**, 353.

EMPIRE RHEUMATISM COUNCIL

MULTI-CENTRE CONTROLLED TRIAL COMPARING CORTISONE ACETATE AND ACETYL SALICYLIC ACID IN THE LONG-TERM TREATMENT OF RHEUMATOID ARTHRITIS*

RESULTS UP TO ONE YEAR

(RECEIVED FOR PUBLICATION OCTOBER 31, 1955)

(1) INTRODUCTION

In the last 6 years cortisone acetate (hereafter designated "cortisone") has been widely used in the treatment of rheumatoid arthritis, but of the numerous studies made on a sufficiently wide scale, only two have made a controlled comparison over a prolonged period between this treatment and another. Both of these trials were carried out at a number of centres in Great Britain under the auspices of the Medical Research Council and the Nuffield Foundation. One dealt with the use of cortisone as an adjuvant to manipulation compared with tablets of aspirin, codeine, and phenacetin (Medical Research Council and Nuffield Foundation, 1954). The second trial compared cortisone with aspirin in the treatment of early cases of rheumatoid arthritis of less than 9 months' duration at the start of treatment (Medical Research Council and Nuffield Foundation, 1954b, 1955). Neither of these trials showed any striking advantage of cortisone over salicylate medication.

These results coincided with the publication of the only controlled trial of hormones and aspirin in rheumatic fever (Joint Report by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the American Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association, 1955) and the findings in this third trial showed no striking overall advantage of hormones over salicylates. The conclusions reached on the basis of these carefully controlled trials caused considerable comment and even surprise, since it is generally agreed that the immediate results of giving patients with rheumatoid arthritis cortisone or corticotrophin are often dramatic. A number of hypotheses were put forward to account for the difference between these results and the often favourable impression gained by physicians in the ordinary treatment of rheumatoid arthritis with hormones. For example, it seemed possible to many people that a different selection of cases would have given results much more favourable to hormones. In particular, it was thought that the patients with early rheumatoid arthritis of between 3 and 9 months' duration which had been selected for the earlier trial might not be of the type to show maximal benefit on hormones compared with salicylates, since, irrespective of the type of therapy, a high proportion of such patients would improve spontaneously. Accordingly, the Empire Rheumatism Council Research Sub-Committee decided to set up another multi-centre controlled trial in patients with rheumatoid arthritis of rather longer duration.

(2) PLAN OF THE TRIAL

The questions which the trial was designed to answer were these:

1. What is the clinical and functional difference between an aspirin-treated group and a cortisone-treated group at the end of 6 months, one year, 2 years, and 3 years from the start of therapy?
2. Is there any significant difference in the radiological progress in the two groups after one year and each subsequent year?

* The Empire Rheumatism Council Sub-Committee conducting the trial was composed as follows:

Dr. E. G. L. Bywaters (*Chairman*)
Dr. W. S. C. Copeman
Dr. J. J. R. Duthie
Dr. E. T. D. Fletcher
Dr. F. Dudley Hart
Dr. G. D. Kersley
Dr. E. Lewis-Faning
Dr. R. M. Mason
Dr. Oswald Savage
Professor R. E. Tunbridge
Dr. H. F. West
Dr. Ifor Williams/ co-opted)

3. How many have to be taken off treatment and why?
4. What is the incidence of the different complications?

One hundred patients were to be selected who had polyarthritis of the rheumatoid type affecting three joints or more, other diseases such as rheumatic fever, Reiter's disease, or Neisserian infection being excluded. It was decided to include patients with rheumatoid arthritis of all durations provided that no gross irreversible change was present in the joints. Every care was taken to exclude patients likely to react unfavourably to hormones. Thus patients of over 60 or under 17 years of age were excluded on account of the possible danger of producing crush fractures or cerebral accidents. Patients with mental instability, symptoms of gastric disease, or hypertension were to be excluded, as well as those whom it was thought would not co-operate in a prolonged trial either because of personality or because of circumstances. Patients in whom the amount of possible improvement was small were also excluded by stipulating that on entry to the trial the patient must be able to walk a few steps before treatment was started and that he should have no fixed flexion deformities of any major degree. It will be seen later that, even with such a careful screening, some difficulties ensued, but it was felt that, if the above criteria for admission were used, one of the criticisms that had been levelled at the earlier trial would no longer be valid.

(3) Allocation of Patients to Treatment

The patients were distributed amongst nine treatment centres and allocation to one of the two treatment groups was made centrally and at random. They were stratified by sex and by centre, thus avoiding any possible unconscious bias in distribution and ensuring a similar sex ratio in each of the two treatment groups and a comparable number of patients in each treatment group for each centre. Similarity of the two treatment groups in respect of age, duration, and the type of onset was not deliberately arranged, but as will be shown in Section 8, a satisfactory similarity between the two groups was achieved, not only in these three respects, but also in regard to other possible differentiating factors.

(4) Treatment Schedule

The treatment was planned to consist of a basic regime of general care, including the use of physiotherapeutic measures and splints, plus, for one group, cortisone acetate and, for the other, aspirin.

Cortisone was to be given initially at a level of 25 mg. by mouth 8-hrly until the maximum effect had been produced and then the dose was to be reduced or increased by not more than 12·5 mg. per day at intervals of not less than one week until the lowest dose which kept that patient largely symptom-free was found. In patients who needed 100 mg. or more daily as a maintenance dose, therapy was discontinued if, after one month, a lower dose could not be used. Patients needing as little as 25 mg. daily after 4 weeks of this dosage discontinued therapy in case natural remission had occurred. If relapse occurred within one month, dosage was restarted at the 75 mg. level, but if relapse occurred after one month without treatment, dosage was started with 25 mg. as before.

Aspirin was to be given in five daily doses at a level of 4 g. per day for at least the first week or until maximum effect was produced, then the dosage was to be adjusted up or down as necessary between 1 and 8 g. per day to the minimum required to restore the maximum functional efficiency possible without side-effects. If aspirin as such was not tolerated, other equivalent preparations of salicylate were permissible.

If therapy of either variety was to be discontinued the drug was to be withdrawn gradually and a note made of the reason. Both groups of patients were told that they were going to be put on to a prolonged course of treatment, but they were not told the name of the particular drug which was to be given.

Table I (opposite) shows the levels of dosage of cortisone and aspirin in the two groups at the start, at 6 months, and at the end of the year, excluding withdrawals. It will be seen that in the 38 patients who completed the year on cortisone the mean dose for the first month of therapy was 75 mg./day; this fell to 72·8 mg. at the 6th month, and 68·7 mg. at the end of the year. The year's fall is statistically significant. The 39 patients who completed the year on aspirin started at a mean level of 58·7 gr. per day; this fell to 56 gr. at 6 months, and rose again to 58·6 gr. at the end of the year.

The details of dosage in the two treatment groups are given in Table II (opposite).

(5) Assessment of Progress

This was deliberately kept as simple as possible. The observations made had to serve two purposes: the statistical comparison, and the clinical control and dosage regulation. Patients were seen and assessed at least twice during the month preceding treatment and subsequently as frequently as necessary. A full examination was to be made monthly for the first 3 months and subsequently 3-monthly.

TABLE I

DOSAGE ANALYSIS

(patients who completed a full year)

Drug	No. of Patients	Starting Dosage (mean of weeks 1-4)	Mid-year Dosage (mean of weeks 25-28)	12-month Dosage (mean of weeks 49-52)
		Mean ± S.E.	Mean ± S.E.	Mean ± S.E.
Cortisone (mg./day)	38	75·0 ± 1·1	72·8 ± 2·4	68·7 ± 2·6
Aspirin (gr./day)	39	58·7 ± 1·4	56·0 ± 3·0	58·6 ± 3·3

TABLE II

DISTRIBUTION OF DOSAGE LEVELS AT BEGINNING OF SURVEY COMPARED WITH THOSE AT 6 MONTHS AND 12 MONTHS

(patients who completed a full year)

Drug	Starting Values (mean of weeks 1-4)	No. of Patients	Dosages at 6 months				Mean at 6 months	Dosages at 12 months				Mean at 12 months
			30–49	50–69	70–79	80 and over		Under 40	40–69	70–79	80 and over	
Cortisone (mg./day)	50–69	5	—	4	1	—	63	—	3	1	1	66
	70–79	29	2	9	10	8	72	3	10	13	3	64
	80 and over	4	—	—	—	4	90	—	—	1	3	86
	Mean Starting Value 75 ..	38	2	13	11	12	73	3	13	15	7	67
			Under 37·5	37·5–52·4	52·5–67·4	67·5–82·4	82·5 and over		Under 37·5	37·5–52·4	52·5–67·4	67·5–82·4	82·5 and over	
Aspirin (gr./day)	Under 37·5	1	1	1	—	—	—	30	1	—	—	—	—	30
	37·5–52·4	7	2	3	1	1	—	47	1	3	2	1	—	51
	52·5–67·4	26	2	7	11	5	1	58	5	3	10	4	4	59
	67·5 and over	5	—	1	2	1	1	66	—	1	2	1	1	66
	Mean Starting Value 59 ..	39	5	11	14	7	2	56	7	7	14	6	5	58

Records were made on a standardized form (Fig. 1, overleaf), which included name, sex, age, occupation, centre, the name of the investigator responsible, the dosage for each week of the trial, the employment status, the functional capacity, a subjective estimate by the patient of his condition, the number of joints affected, haemoglobin concentration, erythrocyte sedimentation rate, and notes of any complications encountered. Details of these assessments were defined as below:

Employment Status.—This was recorded in four grades:

I. Patients fit for their previous employment without adjustments (the occupation was to be noted): the housewife had to be fit for all duties.

II. Patients able to continue their previous employment with certain adjustments; the housewife had to be fit for a modified form of housework.

III. Patients who had had to change to a lighter occupation either with or without new training; the housewife could perform only light duties.

IV. Patients unfit for any form of employment; the housewife unable to do any housework.

Functional Capacity.—This was divided into four categories:

(1) Normal (full physical activity);
(2) Moderate limitation of activity;
(3) Serious limitation of activity;
(4) Routine simple duties impossible, including cases confined to bed or chair.

For the subjective estimate of function the patient was asked to grade his own functional condition at each assessment as one of the following: 100, 75, 50, 25, or 1 per cent. well.

Articular Involvement.—A joint was considered to be involved if it showed two out of the following three symptoms:

(*i*) Tenderness and pain,
(*ii*) Limitation of movement,
(*iii*) Swelling.

E.R.C. SCHEME FOR LONG-TERM CORTISONE/ACETYL-SALICYLIC ACID TRIAL IN RHEUMATOID ARTHRITIS

Name	Sex	Age	Occupation	Centre	Responsible Investigator
	Period before Treatment	Months after Start of Therapy			
		1	2	3	4	5	6 ± ½	7	8	9	10	11	12 ± ½
Date													
Dosage A.S.A. / Cortisone (in wks as g./day)													
Employment Status (I-IV) .. (Note type)													
Functional Capacity (1-4) ..													
Subjective Estimate (1, 25, 50, 75, 100 per cent. well)													
Number of New Joints Affected in Period ..													
Total Number of Affected Joints at Examination													
Hb (g. per cent.)													
Erythrocyte Sedimentation Rate (mm./hr (Wn))													
Radiological Examination (check)													
Complications in Period (specify 1 to 9)													

Footnotes:

Fig. 1.—Proforma used in trial.

For the purpose of counting joints involved, the following 68 joints only were considered: both jaws, sternoclaviculars, acromioclaviculars, shoulders, elbows, wrists and carpal joints, metacarpophalangeal I-V, proximal interphalangeal I-IV, terminal interphalangeal I-V, hips, knees, ankles, tarsal joints, metatarsophalangeal I-V, toes I-V. All other joints or subdivisions were disregarded.

X rays of at least two affected joints and their contralateral pair were to be taken before treatment and repeated subsequently at 6-monthly intervals. A checking space was provided on the form. Assessment of the films was made as detailed below (p. 362).

Haematological Investigations.—These included erythrocyte sedimentation rate (Westergren), and haemoglobin estimations in g. per 100 ml.

Complications and Side-Effects.—These were noted under the following headings and in detail:

(1) Electrolyte changes,
(2) Carbohydrate metabolism,
(3) Disturbance of other endocrine glands,
(4) Personality changes,
(5) Intercurrent infections, tuberculosis, and other diseases,
(6) Injuries such as fractures, ruptured tendons, etc.,
(7) Cardiac changes,
(8) Renal changes,
(9) Blood pressure changes.

(6) WITHDRAWALS FROM THE TRIAL

Patients were to be withdrawn from the trial for three reasons:

(*a*) because they developed serious symptoms due to cortisone or aspirin necessitating discontinuance of that particular drug,

(*b*) because they were deriving no benefit from, or were actually deteriorating on, a drug and in the opinion of the physician needed some other form of therapy. (In addition, patients on cortisone were to be withdrawn if they needed 100 mg./day for more than 1 month.)

(*c*) Because they did not attend hospital for treatment or assessment.

Of the fifty patients allocated initially to each group, one (on cortisone) never attended and is excluded; a further 22 were lost to the trial during the first year, leaving at 6 months a comparison of 45 patients on cortisone and 42 on aspirin, and at the end of the year 38 on cortisone and 39 on aspirin. Table III indicates the reasons for withdrawal in each of the two groups during the first 6 months and the last 6 months of the first year. Five patients were intolerant of aspirin, suffering indigestion or other gastric symptoms. Four patients in the cortisone group developed signs necessitating discontinuation of therapy. Of the two with hypertension, one developed a blood pressure of 145/110 mm. Hg at the fifth month, the other—admitted wrongly to the trial with a blood pressure of 160/110–developed a blood pressure of 200/120 at the tenth month: the hormone was discontinued after this and the blood pressure fell to 175/100 by the end of the year. One developed indigestion, which recurred with an attempt at restarting cortisone. In one patient, the hormone was stopped because of a chest *x* ray showing old inactive tuberculosis.

Deterioration while on aspirin was specifically mentioned in one patient, but may have been a factor in the five others who failed to attend. In the cortisone series, a total of six patients were withdrawn because they derived no benefit from it, and, in fact, deteriorated on the maximum allowed dosage of 100 mg./day. (It will be remembered that this level was put as a ceiling since it was thought possibly dangerous to continue patients for long periods of time at over 100 mg./day.) Two others failed to attend.

The effect of these withdrawals on the composition of the two groups is dealt with in Section 8. After detailed study it did not seem that the loss of these 23 patients disturbed the relative composition of the two groups on entry to the trial to any significant extent.

(7) COMPLICATIONS AND SIDE-EFFECTS

In addition to the complications which resulted in withdrawal of patients from the trial (discussed above), a further eighteen patients on cortisone and seventeen patients on salicylates were recorded as suffering from "complications". Many of these were of a minor nature; it is probable that in some centres similar episodes were not recorded since it is unlikely that they were directly due to hormones (*viz.* coryza).

Cortisone

While weight gain was common, in only four patients was the presence of *oedema* noted, in one case as early as the third month, and in others between the sixth and twelfth months.

Heartburn, flatulence, epigastric discomfort, and pyloro-spasm were seen in four patients at various times, but chiefly towards the end of the second 6 months. In none of them was this serious.

Amenorrhoea was seen in two patients, menorrhagia in one and irregular periods in one.

Mild psychic disturbances mainly depression, were seen in three patients at the beginning of treatment and in one case at the tenth month.

Intercurrent infection occurred in ten patients, but this was of a mild nature (phlebitis, two; upper respiratory infection, three; diarrhoea, two; influenza, one; laryngitis, one; pneumonitis, one; stomatitis and glossitis, one.)

One patient suffered a fracture of the elbow caused by a fall at the fourth month of treatment.

Extra-systoles were heard in one patient from time to time.

In seven patients occasional blood pressure readings

TABLE III

CASES WITHDRAWN IN FIRST YEAR OF TRIAL

Reason for Withdrawal	First Half-year		Last Half-year		Total	
	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin
"Toxicity"*	2	3	2	2	4	5
Deterioration	2	1	4	0	6	1
Non-attendance	1	4	1	1	2	5
Totals	5	8	7	3	12	11

*This includes for Cortisone, two with hypertension, one with indigestion, and one with healed tuberculosis; and for Aspirin, five with indigestion.

in excess of 90 mm. Hg diastolic were recorded (ranging up to 110 mm. Hg).

None of these complications was severe, but these data should be considered in conjunction with those on patients withdrawn from the trial because of complications (see Section 6).

Aspirin

Nausea, tinnitus, vertigo, and vomiting were seen in thirteen patients, indigestion and dyspepsia in four, bleeding due to fibroids in one, and intercurrent upper respiratory infection in four. One patient suffered from angina on effort in the first months, but the electrocardiogram was normal on two occasions. One patient developed a rash on the face and neck in the tenth month. In four patients nausea and tinnitus were present for at least five months and sometimes longer. None of these complications was severe.

These symptoms necessitated usually a slight reduction and in a few a temporary interruption of treatment. Thus the dosage in this trial seemed to be at a level at which complications might occur, but were not of a serious nature.

(8) Comparison of the Cortisone and Aspirin Groups at the Beginning of the Trial

Table IVA shows that the two groups were similar in all relevant factors at the start of the trial. More detailed analysis by sex showed no difference in respect of age, duration, type of onset, mean number of joints affected, erythrocyte sedimentation rate, haemoglobin level, or number withdrawn. All differences referred to throughout this report are considered to be statistically significant when they reach the 0·05 level unless some other specific statement is made.

Duration of Symptoms.—The range for the cortisone group was from 2 to 16 years generally, although one patient had the extreme duration of 28 years (she completed the whole year's course). In the aspirin group the range generally was from 1 to 14 years, with three higher durations of 18, 20, and 22 years. The mean durations in the two groups were very similar: 7·1 and 6·8 years respectively.

Employment Status and Functional Capacity.—The distributions of the two groups by employment grades, and by function—whether measured objectively or subjectively—were very similar (Table VA). To summarize these distributions, "means" have been calculated (although strictly such means are not statistically valid). These "means" are identical or nearly so; χ^2 tests show that the probability of finding such differences as do exist, other than by chance, is very remote.

Effect of Withdrawals on the Composition of the Groups.—As detailed in Table III, during the first 6 months, thirteen patients (five on cortisone and eight on aspirin) were lost to the trial (including the one female previously mentioned who failed to attend). In the second 6 months ten more dropped out (seven on cortisone and three on aspirin).

Thus, at the mid-year, results could be compared for 45 on cortisone and 42 on aspirin, but over the whole year data were available for only 38 on cortisone and 39 on aspirin.

Various tests showed that the loss of these 23 patients did not disturb the composition of the two treatment groups. The similarity of the groups at the beginning of the trial when it was based on the original 99 patients, still held good when tested on the 87 who were present at 6 months, or on the 77 who completed the year, and no real

Table IV

SIMILARITY OF THE TWO TREATMENT GROUPS AT BEGINNING OF TRIAL

Points of Comparison		(A) All Entrants		(B) Excluding Cases Withdrawn during the Year	
		Cortisone	Aspirin	Cortisone	Aspirin
Number of Patients		49 {20 males, 29 females}	50 {20 males, 30 females}	38 {15 males, 23 females}	39 {14 males, 25 females}
Mean Age (yrs)		46·0 ± 1·34	47·0 ± 1·92	44·7 ± 1·67	47·4 ± 1·51
Mean Duration of Symptoms (yrs)		7·1 ± 0·78	6·8 ± 0·75	6·9 ± 0·91	7·6 ± 0·90
Type of Onset	Acute	9	8	6	6
	Non-acute	40	42	32	33
Mean Number of Affected Joints		20·5 ± 2·0	18·0 ± 1·8	19·8 ± 2·28	17·0 ± 1·85
Mean Erythrocyte Sedimentation Rate (mm./hr Westergren)		40·2 ± 3·8	35·8 ± 3·5	37·2 ± 4·2	36·4 ± 4·1
Mean Hb (g. per cent.)		12·6 ± 0·22	12·8 ± 0·19	12·5 ± 0·22	12·5 ±0·27

TABLE V
INITIAL GRADING BY EMPLOYMENT AND FUNCTION

Patients Compared	Employment Status			Functional Capacity					
				Physician's Estimate			Patient's Own Estimate		
	Grade	Cortisone	Aspirin	Grade	Cortisone	Aspirin	Grade (% well)	Cortisone	Aspirin
(A) All Entrants	I (Fit)	5	8	1 (Best)	2	4	100	1	1
	II	24	21	2	31	33	75	10	18
	III	14	15	3	14	10	50	25	23
	IV (Unfit)	6	6	4 (Worst)	2	3	25	12	6
							1	1	2
	Total	49	50	Total ..	49	50	Total ..	49	50
	"Mean"* Grade..	2·4	2·4		2·3	2·3		3·0	2·8
(B) Excluding Cases withdrawn during the Year	I (Fit)	5	6	1 (Best)	2	2	100	1	1
	II	18	17	2	25	27	75	9	14
	III	10	12	3	9	8	50	18	18
	IV (Unfit)	5	4	4 (Worst)	2	2	25	9	5
							1	1	1
	Total	38	39	Total ..	38	39	Total ..	38	39
	"Mean"* Grade..	2·4	2·4		2·3	2·3		3·0	2·8

* The use of the term "mean" here and in Tables VI, VII, VIII, A, and C, is unjustifiable, but convenient as an index to summarize the distribution.

differences between the two groups in regard to the factors examined could be found.

Since comparison of the relative effectiveness of the two types of treatment (cortisone and aspirin) had to be judged mainly by the experience of the 77 who pursued either course for a complete year, it was fortunate that the evidence enabled this conclusion to be reached, as otherwise the loss to the survey of these 23 patients would have seriously prejudiced the results.

Tables IVB and VB summarize this evidence. Just as Tables IVA and VA showed how similar were the two treatment groups as they were originally constituted, so Tables IVB and VB show the similarity of the two treatment groups when those who withdrew were excluded.

Not only do Tables IVB and VB show that, after excluding the withdrawals, the two groups were still alike, but a comparison with Tables IVA and VA will show that the differences between the values of the indices arising out of the removal of those 23 patients were very slight.

(9) RESULTS

Comparison of Progress in the Two Treatment Groups (Tables VI-XIII)

Employment Status.—In this respect (Table VI) the two groups could hardly have remained more stable. There is no significant difference between the two groups at any time nor between either group from one assessment to the next. This is, however, a rather coarse grading.

Functional Capacity

Objective.—As estimated by the physician on the basis of examination and interrogation (Table VII, overleaf), this shows a tendency to improvement in each treatment group during the year, but the improvement is without statistical significance.

It may be of interest to add that only one patient (on aspirin) was up-graded in both half-years.

The lowest section of Table VII takes into account the amount of up-grading and down-grading which was *possible* for each group of patients. This was done by expressing the amount of each change which actually

TABLE VI
DISTRIBUTION BY EMPLOYMENT STATUS

Employment Status	Beginning of Year		Middle of Year		End of Year	
Grade	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin
I (Fit)	5	6	9	12	7	10
II	18	17	20	15	20	17
III	10	12	7	9	9	10
IV (Unfit)	5	4	2	3	2	2
Total Number	38	39	38	39	38	39
"Mean" Grade	2·4	2·4	2·1	2·1	2·2	2·1

TABLE VII

DISTRIBUTION ACCORDING TO FUNCTION (PHYSICIAN'S ESTIMATE) AT BEGINNING, MIDDLE, AND END OF FIRST TREATMENT YEAR (NUMBER UP-GRADED AND DOWN-GRADED IN EACH PERIOD)

Functional Capacity	Beginning of Year		Middle of Year		End of Year	
	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin
1 (Best)	2	2	4	3	6	5
2	25	27	27	29	23	26
3	9	8	6	6	9	8
4 (Worst)	2	2	1	1	—	—
Total	38	39	38	39	38	39
"Mean" Grade	2·3	2·3	2·1	2·1	2·1	2·1
Regrading	**First Half-year**		**Second Half-year**			
Up-graded	10	10	8	5		
Down-graded	3	5	7	4		
No Change	25	24	23	30		
"Actual" as percentage of "Possible" Scores	**First Half-year**		**Second Half-year**		**Complete Year**	
Up-grading	22	20	19	14	24	24
Down-grading	6	7	10	5	6	7

occurred as a percentage of that which was possible. To illustrate the method, let us consider the initial grading of the 38 patients on cortisone: two were Grade I and could not therefore be up-graded at all, 25 were Grade II and each could have moved up one grade (25), nine were Grade III and each of these could have moved up two grades (18), two were Grade IV and could each have improved three grades (6). Thus the total score for up-grading which was possible for this group in the first 6 months was $25 + 18 + 6 = 49$. As it happened, the possible score in the aspirin group was also 49. The former actually improved eleven and the latter ten grades (details are given in the Appendix, Tables A and B), *i.e.* 22 per cent. against 20 per cent. of their possible scores.

Similarly, the possible down-grading score was 65 for the cortisone group and 68 for the aspirin group. In the event, the former deteriorated four points and the latter five points, 6 per cent. and 7 per cent. respectively of their possible scores (Appendix, Tables A and B).

Calculations on a similar basis for the second 6 months showed only slight but non-significant differences between the two groups, and taking the experience over the whole year, there was no difference at all between them. (Details of the actual and possible scores are summarized in the Appendix, Tables A and B.)

Subjective.—As judged by the patient, subjective well-being shows a similar but more marked tendency to improvement which is reached by the end of the first 6 months and maintained to the end of the year (Table VIII, opposite). Details of the actual and possible changes are given in the Appendix, Tables C and D.

Both treatment groups behaved in the same way, and there is no difference between the groups either in distribution or in change of grade, whether considered absolutely or as a percentage of possible change.

Number of Joints Affected.—Table IX compares the mean number of joints affected per patient in each treatment group at the beginning, middle, and end of the year—assessed clinically, not radiologically, out of 68 individually listed joints. There was a small but similar amount of improvement in both groups (Table IX) occurring in the first 6 months of treatment, which reached the level of significance.

TABLE IX

MEAN NUMBER OF JOINTS AFFECTED PER PERSON AT BEGINNING, MIDDLE, AND END OF FIRST YEAR OF TREATMENT (PATIENTS WHO COMPLETED THE YEAR)

Time of Examination	Joints Affected per Person	
	Cortisone	Aspirin
	Mean ± S.E.	Mean ± S.E.
Beginning of Year	19·8 ± 2·3	17·0 ± 1·9
Middle of Year	12·5 ± 1·6	11·2 ± 1·6
End of Year	11·2 ± 1·9	9·3 ± 2·3

At no period was the average number of joints affected (per person) in the two groups significantly different.

Neither initially, at mid-year, nor at the end of the year was there any real difference in the number of joints affected in each group. (An analysis of the *amount* of improvement in the number of joints affected is given in the Appendix, Tables E and F.)

Erythrocyte Sedimentation Rate (mm./hr Westergren).—The mean erythrocyte sedimentation rate

TABLE VIII

DISTRIBUTIONS ACCORDING TO PATIENT'S OWN ASSESSMENT OF HIS CONDITION AT BEGINNING, MIDDLE, AND END OF FIRST YEAR

Grade (per cent. Well)	Beginning of Year		Middle of Year		End of Year	
	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin
100	1	1	5	5	5	4
75	9	14	20	22	20	23
50	18	18	10	10	12	10
25	9	5	3	2	1	2
1	1	1	—	—	—	—
Total	38	39	38	39	38	39
"Mean" (per cent.)	50	56	68	69	69	69
Regrading	**First Half-year**		**Second Half-year**			
Up-graded	26	22	7	7		
Down-graded	3	6	6	8		
No Change	9	11	25	24		
*"Actual" as percentage of "Possible" Scores	First Half-year		Second Half-year		Complete Year	
Up-grading	41	39	16	15	42	35
Down-grading	5	7	6	7	4	5

Both groups show a change in distribution (statistically significant) indicating that many felt better at the middle of the year. This difference is confined to the first half-year and was the same for those on aspirin as for those on cortisone.
* *E.g.* a change from 50 per cent. to 75 per cent. well scored one point.

levels were the same in each group at start, 6 months and 1 year (Table X), some tendency to improvement being seen in the course of the year.

Fig. 2 presents the average erythrocyte sedimentation rate levels at successive monthly intervals after treatment was started. (This was not recorded consistently for each patient *every* month, so that the number of observations available varied from month to month.)

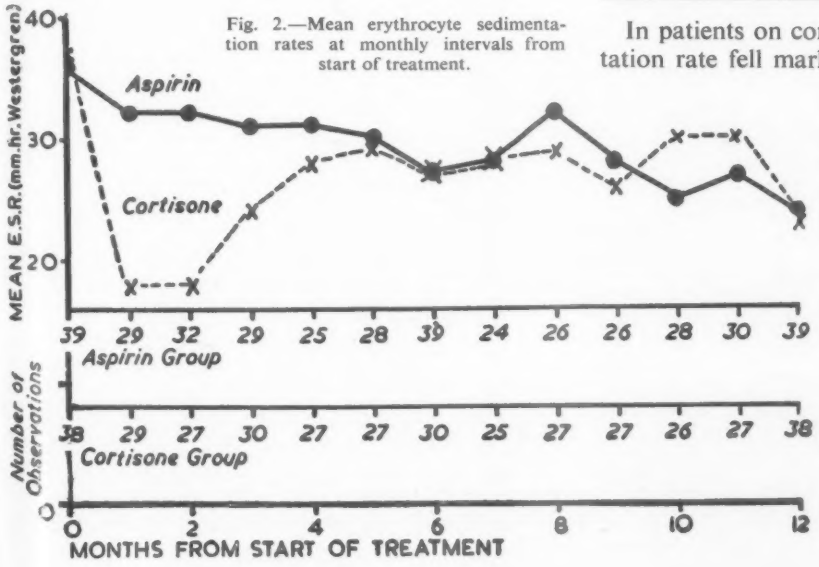

MEAN E.S.R. (mm. hr. Westergren)
40
30
20
Aspirin
Cortisone
39 29 32 29 25 28 39 24 26 26 28 30 39
Aspirin Group
38 29 27 30 27 27 30 25 27 27 26 27 38
Cortisone Group
Number of Observations
0
0 2 4 6 8 10 12
MONTHS FROM START OF TREATMENT

Fig. 2.—Mean erythrocyte sedimentation rates at monthly intervals from start of treatment.

TABLE X

ERYTHROCYTE SEDIMENTATION RATE LEVELS AT BEGINNING, MIDDLE, AND END OF FIRST YEAR
(mm./hr Westergren)

Time of Examination	Cortisone	Aspirin
	Mean ± S.E.	Mean ± S.E.
Beginning of Year ..	37 ± 4	36 ± 4
Middle of Year	27 ± 3	27 ± 3
End of Year	23 ± 3	24 ± 3

In patients on cortisone the erythrocyte sedimentation rate fell markedly in the first 2 months and gradually rose again. (This is in accordance with observations made by other workers.) No such fall in the first and second months was apparent for the aspirin group, which in the aggregate presented a more gradual and regular decline over the year.

No monthly variation similar to that noted above for cortisone patients could be demonstrated in regard to other indices, *viz.* functional activity and haemoglobin levels.

Haemoglobin Level (Table XI).—Both treatment groups had the same rather low average level initially (12·5 g. per cent.). By mid-year this had been increased to 13·3 in the cortisone group, but

TABLE XI
AVERAGE HAEMOGLOBIN LEVELS AT BEGINNING, MIDDLE, AND END OF FIRST YEAR
(g. per cent.)

Time of Examination	Cortisone	Aspirin
	Mean ± S.E.	Mean ± S.E.
Beginning of Year ..	12·5 ± 0·22	12·5 ± 0·27
Middle of Year.. ..	13·3 ± 0·27	12·5 ± 0·31
End of year	13·3 ± 0·15	13·1 ± 0·20

the aspirin group showed no such improvement. In the second half-year the cortisone group showed no change, whilst the aspirin group had improved slightly (not significantly), bringing the averages of the two groups into line by the end of the year.

Analysis of X-Ray Protocols.—The last index of comparison to be presented is that which measured the progression of the disease radiologically.

One year is a short interval in the natural history of rheumatoid arthritis and in the larger joints no change was detected that could not be mimicked or distorted by slight variation in radiographic positioning. With hardly an exception, radiological change occurred entirely in the small joints of the extremities, and for ease of comparison this survey was confined to the wrists and hands.

Of the 77 patients who completed one year in the trial, *x*-ray films of the hands were available initially and at approximately 12 months after treatment for 66 (35 in the cortisone and 31 in the aspirin group). These represented the full range of the disease—from two with no bony changes to ten with major destruction and distortion. Analysis of these 66 patients showed no significant difference in any respect at the start of the trial between the two treatment groups, or between either or both of them and the original total group numbering 99 at the start or 77 at the end of one year.

The assessment was designed to measure the alteration that can be seen in one year, and evidence that could not be reliably obtained from the standard postero-anterior view of the hands and wrist was excluded. The features of osteoporosis, soft tissue swelling, ankylosis, and ulnar deviation which are characteristic of the disease were not used.

In some patients the stress falls on the wrists, in others on the fingers, and some allowance for this was made by using a classification discriminating eight subdivisions of the wrist joint to counterbalance the fourteen joints of the fingers. This division is purely arbitrary and is based on the standard radiograph, taking no account of function and little of conventional anatomy (Fig. 3). With this decision the assessment of the radiological progression was reduced to the measurement of change in 44 small joints, eight in each wrist and fourteen in the fingers of each hand. Each alteration was defined and for some signs two grades of progression were also defined.

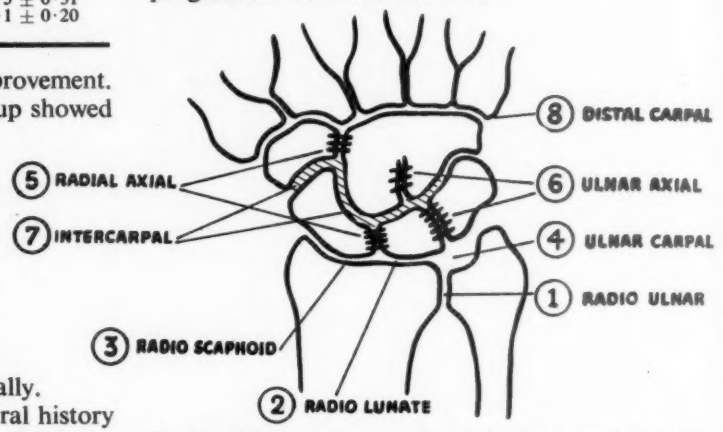


Fig. 3.—Diagram of wrist and carpal joints, showing arbitrary number of joint spaces separately considered for the purpose of *x*-ray analysis.

Five typical signs were used:

(*a*) *Joint Narrowing.*—Critical values were assigned to each joint. At the metacarpophalangeal joint for example, a width of more than 1·5 mm. was said to be normal, below this figure the joint was said to be narrowed. The actual number is of less importance than appears at first sight, since the only alteration that scored was a change from normal to narrowed. Once narrowed—by this definition—further reduction in joint space did not score.

(*b*) *Surface Erosion.*—A surface erosion was said to be present when the cortical white line was no longer visible to the naked eye. An increase in the length of an erosion by up to 2 mm. was counted a slight change, by more than this a marked change. The removal of long stretches of the cortex, 3 or 4 mm. dissolving at a time, is the commonest method of progression in rheumatoid arthritis.

(*c*) *Pocketed and Enclosed Erosions.*—These are erosions of bone which are much deeper than the surface erosions, and most of them are nearly spherical in shape. The pocketed type has a small visible communication with the joint surface, while the enclosed type does not apparently reach the joint surface. If the diameter of the erosions increased by up to 1 mm. the change was said to be slight, by more than this the change was marked.

(*d*) *Periosteal Reaction.*—This was seen to *develop* during the year in only one patient and this was scored as a single point.

(*e*) *Subluxation.*—This was scored (1 point) if it *developed* during the year and was unequivocal.

The most superficial observation of the films will show that each of these signs is open to considerable observer error, and the criteria enumerated above give possibly an exaggerated idea of mathematical exactness. The films were read by one person, a radiologist without knowledge of the treatment group of the patient.

Scoring.—Two alternative methods of scoring progression were used, both quite arbitrary and, indeed, giving equal weight to each joint:

(1) Any deterioration of the 44 joints in any individual could score two points—a total possible score of 88 per patient. A joint scored one point if only slight changes had occurred, but if one or more marked changes were recorded for it, two points were given. By this method, every joint, whether initially affected or not could score two points.

(2) Joints not affected initially scored an additional point if they became affected, so that the total *possible* score varied according to the number of joints initially affected, the maximum possible score (no joints initially affected) being 132. This method seems to be preferable to the former.

In both methods allowance was made for joints which were initially so damaged that further progression was impossible (this reduced the possible score), but it was not possible to discriminate joints which were originally so damaged that they could only "deteriorate" and not "markedly deteriorate".

There were 66 patients, with a total of 2,904 joints; 99 of these joints were considered unassessable for various reasons, leaving a total of 2,805 joints. The changes in the radiographic signs were recorded in the following numbers of joints:

Narrowing: 60
Surface Erosion: Slight, 59; Marked, 141
Pocketed Erosion: Slight, 24; Marked, 39
Subluxation: 4
Periosteal Reaction: 1

It will be seen that the bulk of the scoring came from change in the two types of erosion, that narrowing was responsible for a small proportion of the points, and that subluxation and periosteal reactions were numerically negligible. These features are perhaps accentuated by the method of scoring—since marked change may nullify the score due to a minor change in another radiographic sign if both occur in the same joint. By this empirical scoring system a number was derived that was a measure of the change in the bony appearance of the hands and wrists.

Table XII shows that by either method of scoring the cortisone group in the aggregate could make a possible score of two points more than the aspirin group. This is evidence—but based only on joints of the hands—that in addition to their similarity as regards other factors previously examined, the two groups were very similar as regards severity of the disease.

TABLE XII

SCORE OF *X*-RAY PROGRESSION IN HANDS DURING FIRST YEAR OF TREATMENT OF 35 PATIENTS ON CORTISONE AND 31 PATIENTS ON ASPIRIN

Scoring Method	Score	Cortisone	Aspirin	Difference ± S.E.
		Mean ± S.E.	Mean ± S.E.	
1	Possible ..	86 ± 1·1	84 ± 1·4	2 ± 2·8
	Actual ..	6 ± 1·1	9 ± 1·9	3 ± 2·2
	Actual as Percentage of Possible	7 ± 1·4	11 ± 2·1	4 ± 2·5
2	Possible ..	115 ± 2·2	113 ± 1·8	2 ± 2·8
	Actual ..	7 ± 1·6	12 ± 2·4	5 ± 2·9
	Actual as Percentage of Possible	6 ± 1·4	10 ± 2·1	4 ± 2·5
New Joints Radiologically Involved	Joints not Initially Affected ..	29 ± 1·7	29 ± 1·7	0
	Number of such Joints which later became Involved ..	2 ± 0·6	3 ± 0·7	1 ± 0·9

The mean score for radiological deterioration was, by the first method, six in the cortisone group and nine in the aspirin group—scores equivalent to 7 and 11 per cent. of the respective possible scores. By the second method the average scores were seven in the cortisone group and twelve in the aspirin group—scores equivalent to 6 and 10 per cent. of the respective possible scores.

By both methods the difference between the groups approaches but does not reach significance level—nearly a positive finding, but not conclusive on these numbers.

Referring again to Table XII, it will be seen that on the average 29 new joints in the two hands of the average patient could have become affected in both groups, *i.e.* it was possible for the disease to spread to an equal number of new joints in each group. In the event, it spread to an average of two per patient on cortisone and to three per patient on aspirin, which is not a significant difference.

(10) Concordance between the Measurements of Change

It has been established that, whether judged by change in employment status, functional capacity (objective or subjective), number of joints affected, erythrocyte sedimentation rate, haemoglobin level, or radiological change as separate items, the two groups as a *whole* could hardly have kept more in step over the course of a year, than did these two. To what extent were these measurements in agreement one with another?

For this inquiry the two groups were combined, and it was found that agreement as to whether a patient was up-graded, down-graded, or remained in the same grade, existed between these indices in the following proportions:

Indices Compared	1st Half-year (87 patients)	2nd Half-year (77 patients)
	(per cent.)	(per cent.)
(*a*) Function (objective) and Function (subjective), in	48	68
(*b*) Function (objective) and Employment Status, in	62	75
(*c*) Function (subjective) and Employment Status, in	47	64
(*d*) All Three Indices	30	56

Generally the degree of concordance was higher in the second than in the first half-year.

The extent to which the radiological, laboratory, and clinical assessments were in accord is shown in Tables XIII and XIV.

Taking an erythrocyte sedimentation rate of 20 mm./hr as the upper limit of normality, four groups were formed, according to change in erythrocyte sedimentation rate over the 12 months:

Group	Erythrocyte Sedimentation Rate		Description of Serological Change
	Initial	Final	
1	Normal	Abnormal	Worsening
2	Abnormal	Abnormal	Persistent Abnormality
3	Normal	Normal	Normality
4	Abnormal	Normal	Improvement

In Table XIII, in the aspirin group, the trend of the *x*-ray scores is what might be expected. The highest average score occurred in Group 2 which had a high erythrocyte sedimentation rate both initially and finally. Group 3, in which the erythrocyte sedimentation rate started and finished below 20 mm./hr, has a far smaller score (average 6·4), the difference being statistically significant. Group 4, which really *improved* serologically in that the erythrocyte sedimentation rate fell to below 20 mm./hr, had the lowest score (average 5·2).

Table XIII

CORRELATION BETWEEN CHANGE IN ERYTHROCYTE SEDIMENTATION RATE AND *X*-RAY SCORES

Change in Erythrocyte Sedimentation Rate between Beginning and End of Year	Cortisone		Aspirin	
	Number of Patients	Mean *x*-Ray Score ± S.E.	Number of Patients	Mean *x*-Ray Score ± S.E.
1. *Normal to Raised	2	3·6 ± 3·6	0	—
2. Raised to Raised	15	5·2 ± 1·6	14	15·7 ± 3·5
3. Normal to Normal	7	3·9 ± 1·8	10	6·4 ± 1·5
4. Raised to Normal	11	8·8 ± 3·5	7	5·2 ± 1·6

* An erythrocyte sedimentation rate of 20 mm./hr (Westergren) was taken as the upper limit of normality

No such association can be demonstrated in the cortisone group. The lowest average *x*-ray score occurred in Group 1, which serologically became worse, and the highest in Group 4, which serologically improved (*i.e.* whose erythrocyte sedimentation rate changed from abnormal to normal).

When the index "functional activity (objective)" is compared with the *x*-ray score, a more logical relationship appears (Table XIV, opposite). Those up-graded, judged by this index, scored on the average less by *x*-ray assessment (3·9 per cent. of the possible score) than those whose function did not change (9 per cent.), and those who were down-graded showed a still higher average (11·1 per cent.).

Yet even this association is not beyond doubt, since only the increase in average *x*-ray score of the "no change" group over the "up-graded" group was statistically significant.

Furthermore, when the cortisone and aspirin groups are considered separately, this trend in the averages is not seen in the aspirin group (probably because of the very few patients who were down-graded) and again the differences are not significant. Even if the "down-graded" group is included with the "no change" group, so that the comparison is between those who improved clinically and those who did not, no significant difference in the average *x*-ray scores can be demonstrated in the cortisone group.

The Proportion who Improved.—It may be asked what proportion of these patients unequivocally improved under these courses of treatment? The answer depends on how improvement is to be judged. Is it to be judged by improvement in functional activity, on how the patients themselves said they felt, on employment status, or on a combination of these with other clinical assessments? Table XV (opposite) presents some data on this aspect of the inquiry. There is no significant differ-

TABLE XIV

ASSOCIATION BETWEEN CHANGE IN FUNCTION ASSESSED OBJECTIVELY, AND *X*-RAY SCORE
Mean *x*-ray Scores. (Actual as percentage of Possible)

Change in Functional Capacity (objective) over 12 months	Cortisone		Aspirin		All Patients	
	No. of Patients	Mean ± S.E.	No. of Patients	Mean ± S.E.	No. of Patients	Mean ± S.E.
Up-graded	10	3·8% ± 1·6	6	4·0% ± 1·7 s	16	3·9% ± 1·2 s
No Change	21	5·4% ± 1·3	21	12·6% ± 2·8 s	42	9·0% ± 1·6 s
Down-graded	4	14·4% ± 9·0	4	7·7% ± 3·5	8	11·1% ± 4·6

s = Significant increase in *x*-ray scores.

TABLE XV

NUMBER AND PERCENTAGE OF PATIENTS WHO "IMPROVED" AS JUDGED BY VARIOUS CRITERIA

Criterion			Numbers Up-graded							
			First Half-year		Second Half-year		Both Half-years		Complete Year	
			Number of Patients	Per cent.	Number of Patients	Per cent.	Number of Patients	Per cent.	Number of Patients	Per cent.
Employment Status		Cortisone	14	37	4	11	0	0	11	29
		Aspirin	13	33	5	13	2	5	13	33
Function	Objective	Cortisone	10	26	8	21	0	0	11	29
		Aspirin	10	26	5	13	1	3	10	26
	Subjective	Cortisone	26	68	7	18	4	11	25	66
		Aspirin	22	56	7	18	3	8	18	46
All Three Criteria		Cortisone	5	13	2	5	0	0	5	13
		Aspirin	4	10	1	3	1	3	7	18

ence between the aspirin and cortisone groups. More patients in both groups improved in the first 6 months than in the last.

Only five patients on cortisone and four on aspirin recorded improvement by all three functional criteria in the first half-year (13 and 10 per cent. respectively); in the second half-year only two on cortisone and one on aspirin did so (5 and 3 per cent.); no patient on cortisone, and only one on aspirin recorded improvement on all three factors in *both* half-years, but when the final assessments were compared with the initial ones five patients on cortisone and seven on aspirin were found to have improved over the year in all three factors—(13 and 18 per cent. respectively).

Thus, whilst no patient on cortisone showed consistent improvement throughout the year, five maintained what improvement had been established. One patient on aspirin showed improvement in both half-years, and seven maintained the improvement accomplished.

A comparison of the clinical records of these patients who really improved by all three functional criteria with those of the remainder of their group might have been worthwhile had the numbers who improved been greater; on five cases alone no useful purpose could be envisaged.

(11) Discussion

In all prolonged therapeutic trials of any size, some patients disappear, some fail to report at the correct times, and others have to have the regime changed for purely therapeutic reasons. It is fortunate if these inevitable withdrawals are few and are so distributed that they do not affect the relative composition of the groups under investigation. In this trial, if the withdrawals had differentially affected the composition of the two treatment groups to any significant extent, we should have been unable to give an answer to Question 1. Similarly, if the non-availability of *x*-rays in eleven out of 77 patients had altered the composition of either group in relation to the other, we should have been unable to answer Question 2.

Question 1.—*What is the clinical and functional difference between an aspirin-treated group and a cortisone-treated group at the end of 6 months, one*

year, 2 years, and 3 years from the start of therapy? While it is too early yet to give the results for the second and third years, the answer for 6 months and one year from the start of treatment is that there was no clinical or functional difference between the two groups. This holds for employment status, functional capacity (whether estimated by the physician or by the patient), and number of joints involved. The only two significant differences encountered were:

(*a*) Decrease in erythrocyte sedimentation rate in the cortisone group for the first 2 months not seen in the aspirin group; this difference had disappeared at 6 months and one year;

(*b*) Rise in the haemoglobin content of the blood in the cortisone group at 6 months not seen in the aspirin group; this had also disappeared by one year.

There is, in fact, a striking similarity to the results of the M.R.C. Nuffield trial in patients with a duration at start of therapy of between 3 and 9 months. The one significant difference there between the hormone and aspirin groups concerned the haemoglobin level and that had disappeared by the end of the second year.

Question 2.—*Is there any significant difference in the radiological progress in the two groups after one year and each subsequent year?* There was no difference between the two groups at the end of one year that could not arise from chance at the 5 per cent. probability level. The aspirin group showed on the average fresh involvement of three out of 29 initially unaffected joints as compared with two in the cortisone group. It is to be noted that this refers primarily to erosions; osteoporosis, which is notoriously difficult to assess, was not considered.

No combination of the various criteria showed any significant difference between the two groups. The Tables show, however, that taking both groups together, a separate overall improvement did occur in these patients, mostly in the first 6 months of the year. This is most marked according to the patient's own assessment, but is also visible in the "objective" figures, the mean number of joints affected, the erythrocyte sedimentation rate, the Hb level, and to a lesser extent in the physician's estimate of function; it is only absent by the criteria used for assessing employment status which are relatively coarse. Deterioration in either or both groups is seen only in the *x*-ray analysis.

Question 3.—*How many have had to be taken off treatment and why?* is of interest not only as regards the cortisone group, but also by comparison with the aspirin group. A total of nearly one-quarter of the patients had to be withdrawn during the year, but these were equally divided between the cortisone and aspirin groups. Most of these withdrawals were made because either the physician or the patient or both found no evidence of benefit from the allotted drug, so that the patient failed to attend or was changed by his physician to some other treatment. Only one patient on aspirin was specifically withdrawn because of deterioration, as against 6 on cortisone, who were withdrawn because deterioration occurred at the maximum allowed dose. Of the four cases on cortisone which were withdrawn because of toxicity, two had been wrongly entered in the trial, one having pre-existing mild hypertension and one possible evidence of old tuberculosis; the other two developed indigestion and hypertension respectively. Thus, it seems that the selected dosage schedule was a safe one. It corresponds over the course of the year with that given spontaneously for this disease by physicians all over the world as evidenced by published statements. Both this dosage schedule with its upper limit and the freely-chosen dosage constitute a compromise between the maximum dose which avoids serious complications and the minimum dose needed to produce beneficial effects. Thus may be answered the possible criticism that the dosage level of hormone in this trial was too low to be compared adequately with aspirin.

Question 4.—*What is the incidence of the different complications?* No severe complications occurred except those in the two patients on cortisone and the one on aspirin, who were withdrawn because of toxicity. In the cortisone group, oedema, hypertension, indigestion, and depression were the main troubles encountered, which corresponds with general experience.

Finally, the only possible generalization on the long-term treatment of rheumatoid arthritis to be drawn from the results of this trial is that either aspirin or cortisone plus a basic regime of general care, including physiotherapy and splints, will produce improvement in patients carefully selected to avoid the possibility of untoward complications and the likelihood of a failure to respond (on account of ankylosis, etc.). It seems possible that analogues of both the drugs used might be found which would give a higher ratio of benefit to toxicity, but each would have to be tested along similar strictly controlled lines.

From our experience in this trial the following possible modifications of future trial procedure may be deduced:

(*i*) a shortening of the trial period to 6 months;

(*ii*) a change-over at this time to the other trial drug, so as to allow each patient to act as his own control;

(*iii*) a control group, run concurrently with the main trial, which would permit retrospective comparison with one of the two present groups.

(12) Conclusion

There is no significant difference after one year's treatment between two similar groups of patients, one treated with aspirin, the other with cortisone, and both on a similar basic regime of general care. Clinical improvement and radiological deterioration occurred to a similar extent in both groups.

(13) Summary

(1) A therapeutic trial comparing cortisone acetate and aspirin in the long-term treatment of established rheumatoid arthritis was set up by the Research Sub-Committee of the Empire Rheumatism Council.

(2) It was conducted at nine treatment centres with considerable experience of controlled therapy in England and Scotland.

(3) One hundred patients were selected with rheumatoid arthritis affecting three joints or more, between the ages of 17 and 60, excluding those known to have mental instability, gastric disease, or hypertension, and those unlikely to co-operate in a prolonged trial. They were to be able to walk a few steps and to have no fixed flexion deformity of any major degree.

(4) Allocation to one of the two treatment groups was made centrally and at random, stratifying by sex and treatment centre.

(5) Treatment consisted of a basic regime of general care (including physiotherapy and splintage) plus either cortisone or aspirin. Cortisone dosage started at 75 mg./day and was then adjusted up or down until the lowest dose was found which kept that patient largely symptom-free. Therapy was discontinued in patients who needed 100 mg./day or more for more than one month. Aspirin was given at 4 g./day and then adjusted up or down as necessary. The mean dosage at the end of one year for those still in the trial was 69 mg./day cortisone and 59 gr./day (4 g.) aspirin.

(6) 22 patients were withdrawn from the trial during the year (and one failed to start), because of toxicity, failure to benefit, or non-attendance: this affected both treatment groups equally.

(7) The composition of the two groups initially was similar, whether those 99 who started or only those 77 who finished the year are considered, in regard to age, sex, duration of symptoms, type of onset, number of joints affected, employment status, functional capacity (both objectively and subjectively rated), erythrocyte sedimentation rate, haemoglobin level, and radiological evidence of disease in the hands.

(8) Using the above criteria, the results at 6 months and one year showed no significant difference between the two groups, except for the haemoglobin level at 6 months which was better in the cortisone group.

(9) Complications were not severe, apart from two patients with hypertension and one with indigestion on cortisone, and five with indigestion on aspirin, all severe enough to require withdrawal from the trial.

The following centres took part in the trial and the thanks of the Committee are due to their colleagues, both listed and unlisted, at the various centres who assisted in the work:

1. *Hammersmith Hospital*
   E. G. L. Bywaters, G. R. Fearnley, A. Aronoff.
2. *Westminster Hospital*
   F. Dudley Hart, J. Leonard, A. L. Johnson.
3. *Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases*
   H. F. West, M. Fisher.
4. *Royal National Hospital for Rheumatic Diseases, Bath*
   G. D. Kersley, L. Mandel.
5. *Northern General Hospital, Edinburgh*
   J. J. R. Duthie, J. L. Potter, J. D. E. Knox.
6. *West London Hospital*
   O. Savage, M. Joule.
7. *Arthur Stanley Institute, Middlesex Hospital*
   O. Savage, C. E. Quin.
8. *General Infirmary, Leeds*
   R. E. Tunbridge.
9. *Royal Free Hospital*
   E. T. D. Fletcher, J. H. Jacobs.

Messrs. Merck and Co. Inc. kindly supplied the cortisone acetate and the Committee expresses its gratitude to them for this.

Dr. E. Lewis-Faning was responsible for the statistical analysis and Dr. Ifor Williams for designing the *x*-ray analysis and for reading the data. Mr. Victor Howell and his staff at the Empire Rheumatism Council Headquarters were responsible for the not inconsiderable secretarial work.

REFERENCES

M.R.C. and Nuffield Foundation (1954a). *Brit. med. J.*, Joint Report on Cortisone and Codeine, 1, 233.

—— —— (1954b). *Ibid.*, First Joint Report on Cortisone and Aspirin, 1, 1223.

—— —— (1955). *Ibid.*, Second Joint Report on Cortisone and Aspirin, 2, 695.

Essai comparé et contrôlé dans plusieurs centres de l'acétate de cortisone et de l'acide acétyl-salicylique dans le traitement de longue durée de l'arthrite rhumatismale

Résultats de la première année

RÉSUMÉ

(1) Le Sous-Comité de Recherches de l'*Empire Rheumatism Council* institua un essai thérapeutique comparé de l'acétate de cortisone et de l'aspirine dans le traitement de longue durée de l'arthrite rhumatismale manifeste.

(2) L'essai fut effectué dans neuf centres de traitement ayant eu une expérience considérable de la thérapie contrôlée en Angleterre et en Ecosse.

(3) On choisit cent sujets souffrant d'arthrite rhumatismale portant sur trois articulations ou plus et âgés de 17 à 60 ans. On exclut de ce lot tous seux qu'on savait atteints d'instabilité mentale, de maladie d'estomac ou d'hypertension et ceux dont la participation à un essai prolongé était peu probable. Tous devaient povoir marcher quelques pas et ne pas avoir d'enraidissement en flexion trop prononcé.

(4) Une authorité centrale se chargea d'assigner les malades aux deux groupes de traitement en tirant au sort pour chaque sexe dans chaque centre.

(5) Le traitement consistait d'un régime essentiel de soins généraux (y compris la physiothérapie et les prothèses) plus la cortisone ou l'aspirine. Pour la cortisone, on commençait par 75 mg. par jour et on augmentait ou diminuait la dose jusqu'à arriver à la plus faible capable de supprimer la majorité des symptômes. On arrêtait le traitement chez ces malades qui avaient besoin de 100 mg. ou plus par jour pendant plus d'un mois. Pour l'aspirine, on commençait par 4 g. et on ajustait la dose. Au bout d'un an, chez ceux qui participaient encore à l'essai, la dose moyenne par jour était de 69 mg. de cortisone pour les uns et de 4 g. d'aspirine pour les autres.

(6) Au cours de l'année on mit en dehors de l'enquête 22 malades (un autre faillit d'y entrer) en raison de toxicité, d'insuccès ou d'absence; les deux groupes de traitement furent frappées d'une manière égale.

(7) La composition initiale des deux groupes fut similaire aussi bien pour les 99 entrants que pour les 77 restants au bout de l'an en ce qui concerne: âge, sexe, durée des symptômes, type du début, nombre d'articulations atteintes, position occupationnelle, capacité fonctionnelle (mesurée objectivement et subjectivement), sédimentation globulaire, taux d'hémoglobine et critère radiologique de l'atteinte des mains.

(8) Les résultats, basés sur les critères énumérés ci-dessus, de six mois et d'un an, montrent qu'il n'y a pas de différence significative entre les deux groupes, sauf pour le taux d'hémoglobine, plus favorable au bout de 6 mois dans le groupe traité par la cortisone.

(9) Les complications ne furent pas sévères, sauf dans deux cas d'hypertension et un d'indigestion parmi les traités par l'aspirine. La sévérité de ces cas fut suffisante pour les soustraire à l'essai.

Ensayo comparado y controlado, en varios centros, del acetado de cortisona y del ácido acetil-salicílico en el tratamiento de largo plazo de la artritis reumatoide

Resultados hasta un año

SUMARIO

(1) La Subcomisión de Investigaciones del *Empire Rheumatism Council* instituyó un ensayo terapéutico comparado del acetato de cortisona y de la aspirina en el tratamiento de largo plazo de la artritis reumatoide manifesta.

(2) El ensayo fué efectuado en nueve centros de tratamiento con experiencia considerable de la terapia controlada en Inglaterra y Escocia.

(3) Se eligieron 100 sujetos con artritis reumatoide en tres o más articulaciones, entre 17 y 60 años de edad. Se excluyeron los con inestabilidad mental, con enfermedad gástrica y con hipertension así como aquellos cuya cooperación en un ensayo prolongado no fué cierta. Todos debieron poder andar algunos pasos y no tener deformidad en flexión con rigidez pronunciada.

(4) La distribución de los sujetos entre ambos grupos de tratamiento se hizo centralmente y al azar, pero con consideración de sexo en cada centro.

(5) El tratamiento consistía de un régimen básico de cuidados generales (que incluyeron la fisioterapia y el entablamento) y, además, de cortisona o de aspirina. Los tratados con cortisona empezaban con 75 mg. al día, aumentando o disminuyendo la dosis, hasta alcanzar la más pequeña capaz de suprimir la mayoría de los síntomas. Se cesaba el tratamiento en aquellos que necesitaban 100 mg. o más de cortisona al día durante más de un mes. En los tratados con aspirina se empezaba con 4 g. al día y luego se ajustaba la dosis. Al cabo del año, para los que quedaron, la dosis díaria media de cortisona fué de 69 mg. y la de aspirina de 4 g.

(6) Durante el año, se retiraron del ensayo 22 enfermos (uno, además, no llegó a empazar) a causa de toxicidad, beneficio inadecuado o ausencias; ambos grupos fueron igualmente afectados.

(7) La composición inicial de ambos grupos fué similar, tanto para los 99 entrantes como para los 77 restantes al cabo de un año respecto a: edad, sexo, duración de los síntomas, tipo de comienzo, número de articulaciones comprometidas, estado de ocupación, capacidad funcional (determinada objetiva y subjetivamente), sedimentación globular, cifras de hemoglobina y criterio radiológico del compromiso de las manos.

(8) Los resultados, según los criterios mencionados, de 6 meses y de año, muestran que no hubo diferencia significativa entre los grupos, a excepción de las cifras de hemoglobina, a los 6 meses más favorables en el grupo tratado con cortisona.

(9) Las complicaciones no fueron graves, fuera de dos casas con hipertensión y uno con indigestión en el grupo de cortisona y de cinco con indigestión en el grupo de aspirina. Estos casos fueron bastante graves para retirarlos del ensayo.

APPENDIX

Details of Changes in Indices of Comparison

Table A shows the change in grading of functional capacity (physician's estimate) during each half-year. Before the start of therapy the 38 patients on cortisone were graded according to the definitions set out in Section 5. Two were Grade 1, 25 were Grade 2, nine were Grade 3, and two were Grade 4.

At the mid-year assessment, one of the two patients who were originally Grade 1 had deteriorated two grades and the other was unchanged. Of the 25 who were originally Grade 2, two had deteriorated one stage to Grade 3, 21 were unchanged, and two had improved one stage to Grade 1. Of the nine who were originally Grade 3, two were unchanged, six had improved one stage to Grade 2, and one had improved two stages to Grade 1. Of the two who were originally Grade 4, one was unchanged, and one had improved one stage to Grade 3.

As a result of these changes the mid-year distribution was as given in the central column of Table A. The actual score for improvement was eleven (nine had improved one stage, and one had improved two stages). The actual score for deterioration was four (two had deteriorated one stage and one had deteriorated two stages).

The changes in the aspirin group and also the changes in both groups in the second 6 months are to be read in the same manner. The actual and possible scores are summarized in Table B. Tables C, D, E, and F are to be read similarly.

Appendix Table A

DISTRIBUTIONS ACCORDING TO FUNCTIONAL CAPACITY (PHYSICIAN'S ESTIMATE) AT BEGINNING, MIDDLE, AND END OF FIRST YEAR, WITH NUMBER OF GRADES IMPROVED OR DETERIORATED IN EACH HALF-YEAR

Drug	Functional Grade	Distribution at Start	First Half-year: No. of Grades Deteriorated or Improved					Distribution at 6 months	Second Half-year: No. of Grades Deteriorated or Improved					Distribution at 12 months
			−2	−1	0	+1	+ 2		−2	−1	0	+1	+2	
Cortisone	1 (Best)	2	1	—	1	—	—	4	—	2	2	—	—	6
	2	25	—	2	21	2	—	27	—	5	18	4	—	23
	3	9	—	—	2	6	1	6	—	—	3	3	—	9
	4 (Worst)	2	—	—	1	1	—	1	—	—	—	1	—	—
	Total	38	1	2	25	9	1	38	—	7	23	8	—	38
	"Mean" Grade ..	2·3						2·1						2·1
Aspirin	1 (Best)	2	—	2	—	—	—	3	—	—	3	—	—	5
	2	27	—	2	22	3	—	29	—	4	24	1	—	26
	3	8	—	1	2	5	—	6	—	—	3	2	1	8
	4 (Worst)	2	—	—	—	2	—	1	—	—	—	1	—	—
	Total	39	—	5	24	10	—	39	—	4	30	4	1	39
	"Mean" Grade ..	2·3						2·1						2·1

Appendix Table B

FUNCTIONAL CAPACITY (OBJECTIVE—PHYSICIAN'S ESTIMATE)

Actual score (grades improved or deteriorated) and percentage of possible improvement and deterioration in each half-year.

Change	Score	First Half-year		Second Half-year		Complete Year	
		Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin
Improvement	Actual	11	10	8	6	12	12
	Possible	49	49	42	44	49	49
	Actual as percentage of Possible ..	22	20	19	14	24	24
Deterioration	Actual	4	5	7	4	4	5
	Possible	65	68	72	73	65	68
	Actual as percentage of Possible ..	6	7	10	5	6	7

APPENDIX TABLE C

DISTRIBUTIONS ACCORDING TO PATIENT'S OWN ESTIMATE OF HIS HEALTH AT BEGINNING, MIDDLE, AND END OF FIRST YEAR, WITH NUMBER OF GRADES IMPROVED OR DETERIORATED IN EACH HALF-YEAR

Drug	Grade (per cent. Well)	Distribution at Start	First Half-year: No. of Grades Deteriorated or Improved						Distribution at 6 months	Second Half-year: No. of Grades Deteriorated or Improved					Distribution at 12 months
			−2	−1	0	+1	+2	+3		−2	−1	0	+1	+2	
Cortisone	100	1	—	—	1	—	—	—	5	—	3	2	—	—	5
	75	9	1	1	5	2	—	—	20	—	3	15	2	—	20
	50	18	—	1	3	12	2	—	10	—	—	7	2	1	12
	25	9	—	—	—	6	3	—	3	—	—	1	2	—	1
	1	1	—	—	—	1	—	—	—	—	—	—	—	—	—
	Total	38	1	2	9	21	5	—	38	—	6	25	6	1	38
	"Mean" (per cent.)	50							68						69
Aspirin	100	1	—	1	—	—	—	—	5	—	2	3	—	—	4
	75	14	—	4	8	2	—	—	22	—	5	16	1	—	23
	50	18	—	1	3	12	2	—	10	—	1	4	5	—	10
	25	5	—	—	—	3	1	1	2	—	—	1	1	—	2
	1	1	—	—	—	1	—	—	—	—	—	—	—	—	—
	Total	39	—	6	11	18	3	1	39	—	8	24	7	—	39
	"Mean" (per cent.)	56							69						69

APPENDIX TABLE D

FUNCTIONAL CAPACITY (SUBJECTIVE—PATIENT'S OWN ESTIMATE)

Actual score (grades improved or deteriorated) and percentage of possible improvement and deterioration in each half-year.

Change	Score	First Half-year		Second Half-year		Complete Year	
		Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin
Improvement	Actual	31	27	8	7	32	24
	Possible	76	69	49	48	76	69
	Actual as percentage of Possible ..	41	39	16	15	42	35
Deterioration	Actual	4	6	6	8	3	4
	Possible	76	87	103	108	76	87
	Actual as percentage of Possible ..	5	7	6	7	4	5

APPENDIX TABLE E

ACTUAL MEAN REDUCTION IN EACH HALF-YEAR IN NUMBER OF JOINTS AFFECTED

Period Covered	Cortisone		Aspirin		Difference/S.E.
	No. of Patients	Mean ± S.E.	No. of Patients	Mean ± S.E.	
First Half-year	38	7·3 ± 1·6	39	5·8 ± 1·3	1·5/2·1
Second Half-year	38	1·3 ± 1·2	39	1·9 ± 0·9	0·6/1·5
Complete Year	38	8·6 ± 1·4	39	7·7 ± 1·5	0·9/2·1

APPENDIX TABLE F

MEAN NUMBER OF JOINTS AFFECTED AT END OF EACH PERIOD AS A PERCENTAGE OF NUMBER AT BEGINNING OF THAT PERIOD

Period Covered	Cortisone		Aspirin		Difference/S.E.
	No. of Patients	Mean ± S.E.	No. of Patients	Mean ± S.E.	
First Half-year	38	67 ± 7·2	39	68 ± 6·2	1·2/10
Second Half-year	38	101 ± 13·3	39	87 ± 8·8	14·3/15·9
Complete Year	38	56 ± 6·7	39	58 ± 6·0	2/9

Ann. rheum. Dis. (1955), **14**, 371.

HISTOLOGICAL AND CLINICAL EVOLUTION OF LUPUS NEPHRITIS*†

BY

ROBERT C. MUEHRCKE, ROBERT M. KARK, CONRAD L. PIRANI, VICTOR E. POLLAK, AND IRVING E. STECK

From the Departments of Medicine, Presbyterian Hospital, Research and Educational Hospitals, and Cook County Hospital, Chicago, and the Department of Pathology of the University of Illinois College of Medicine

(RECEIVED FOR PUBLICATION JUNE 23, 1955)

In recent years, lupus nephritis has become the major complication and the most pressing problem in patients suffering from lupus erythematosus disseminatus. The clinical course of the disease was different 15 years ago, when Keith (1940) wrote that "renal insufficiency does not play an important role in causing death". At that time patients usually died of a "lupus crisis" or as a result of concurrent infection. However, the use of antibiotics, blood transfusions, balanced water and electrolyte therapy, steroid hormone therapy, and injections of corticotropin has, apparently, prolonged life in those afflicted with systemic lupus erythematosus (S.L.E.). With present methods of care many such patients can usually be kept free of symptoms for a considerable length of time, only to succumb to a rapidly progressive renal failure.

Because of the problems raised by the increased incidence of lupus nephritis, a study of the histological evolution of renal involvement in S.L.E. was begun, using serial percutaneous renal biopsies (Kark and Muehrcke, 1954; Muehrcke and others, 1955a). Histological data were correlated with changing clinical status, clinical laboratory data, and renal function tests in a continuing study of the pathophysiology and natural history of lupus nephritis. Preliminary observations have been reported elsewhere (Pirani and others, 1954; Muehrcke and others, 1955b). This communication outlines some observations on 34 patients studied intensively during the past 18 months.

* Supported in part by a grant from the United States Public Health Service, National Institutes of Health, Bethesda, Maryland (H-1029), and by a grant from Eli Lilly and Company, Indianapolis, Indiana.

† Presented at the annual general meeting of the American Rheumatism Association, 1955. See p. 413 of this issue for discussion.

Methods

Selection of Patients.—34 patients with S.L.E. were studied from the medical services of three hospitals. The diagnosis was established in these patients by the characteristic findings listed in the Table. At least four clinical and four laboratory findings were present simultaneously in the same patient during the course of the illness, and most of the findings listed were present at some stage of the illness. Hargraves's cells (Hargraves and others, 1948) were found in the bone marrow or in the peripheral blood of thirty patients. In three of the four patients in whom Hargraves's cells were not found, histological study of the skin revealed findings compatible with L.E.

TABLE

DIAGNOSTIC CRITERIA USED IN THE SELECTION OF PATIENTS ILL WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Clinical	Laboratory
1. Arthralgia and arthritis	1. Skin or renal biopsy compatible with L.E.
2. Fever	2. Hargraves's cells
3. Serositis	3. Leucopenia, anaemia, or thrombocytopenia
4. Dermatological lesions (face, hair, nails, body surface, mucous membranes)	4. Urinary abnormalities
5. Raynaud's phenomenon	5. Raised erythrocyte sedimentation rate
6. Sensitivity to sunlight	6. Positive thymol turbidity test; other tests of liver function normal
7. Splenomegaly and/or hepatomegaly	7. Increased serum globulin levels
8. Remissions and exacerbations	8. Positive serological tests for syphilis
	9. Positive Coombs' test

Clinical and Laboratory Observations.—All patients were admitted to hospital for study and were followed in a special clinic. The following measurements were made on admission, and these studies were repeated from time to time:

Urine analysis and urinary cultures;
Haematogram, including examination for Hargraves's cells;
Study of bleeding and clotting mechanism;
Determination of serum protein and cholesterol levels;
X rays of kidney;
Standard urea and creatinine clearance tests;
Measurement of 15 min. excretion of phenolsulphonephthalein;
Specific gravity concentration test;
Measurement of 24-hr excretion of urinary protein;
Liver function tests, including measurement of serum cholinesterase;
Measurement of blood urea nitrogen, non-protein nitrogen, and creatinine.

Discrete renal function tests were also done in a few patients.

Percutaneous Renal Biopsies.—These were done with the patient in a prone position. Details of the renal biopsy technique have been described elsewhere (Kark and Muehrcke, 1954; Muehrcke and others, 1955a).

The cylinder of renal tissue was divided into two portions. The first portion—a small piece of tissue—was placed in beef broth culture medium which was later examined for bacterial growth. The second and larger portion was fixed in 10 per cent. neutral formalin in saline. The sections were cut at 6 μ and stained with haematoxylin and eosin, periodic acid fuchsin, and Mallory stain. At times formalin fixed specimens were frozen, cut, and stained with oil-red-O for lipids.

A total of 61 percutaneous renal biopsies were done, usually when the patients were afebrile; 22 patients had serial renal biopsies. No serious complications followed the biopsies. All the cultures of biopsy tissue in beef broth were sterile. Six patients in whom biopsies had been done died later, and autopsies were done on three of them.

Histological Evolution of Lupus Nephritis

The earliest detectable histological lesions in the tissue were found in the glomeruli. These consisted of minute foci of hypercellularity at the periphery of the glomerular tufts (Fig. 1). These lesions were the result of endothelial cell proliferation and at times were associated with localized fibrinoid changes in the glomerular basement membrane. At this stage of lupus nephritis the tubules, blood vessels, and interstitial tissue were usually normal.

The early glomerular lesion was very similar in appearance to the lesions described by Stickney and Keith (1940). We have named this lesion "local glomerulitis" (Fig. 1). "Local"—because, initially, the lesion consisted of one or two patches of proliferating endothelial cells near the periphery of the tuft of some glomeruli. Eventually every glomerulus in the kidney became involved in this process. The term "focal glomerulitis" was not used to describe this lesion because it refers to a disease process which involves only a few glomeruli at any one time and never exists as a diffuse, widespread lesion involving all glomeruli.

As the patches of local hypercellularity in each glomerular tuft increased in size, the glomeruli became ischaemic, a few inflammatory cells appeared, and early necrotic changes and karyorrhexis were noted in the patch of cells (Fig. 2-A). As the local glomerulitis progressed, small fibrinous synechiae were seen bridging Bowman's space (Fig. 2-B) and joining the glomerular tufts to Bowman's capsule. Later, dense fibrous adhesions replaced the synechiae. These histological findings simulated the lesions of focal embolic glomerulonephritis (Fig. 2-A).

As the lupus nephritis progressed, the patchy areas of hypercellularity became more numerous and fused together to involve the whole glomerulus. More and more glomeruli became completely involved in the process. Eosinophilic thickening of the glomerular basement was also noted. Studies with periodic acid fuchsin stain indicated that this eosinophilic material was a mucopolysaccharide. We have named the widespread involvement of glomerular tufts in the process of endothelial proliferation, the "general glomerulitis" stage of lupus nephritis (Fig. 3, opposite).

In some patients, the hypercellularity was a prominent finding, while in others, fibrinoid thickening of the glomerular basement membrane was much more striking, and endothelial cell proliferation was less marked. This stage of local fibrinoid thickening of the glomerular capillary membrane is referred to as a "local membranous glomerulonephritis" (Fig. 4-A, overleaf).

Baehr, Klemperer, and Schifrin (1935) originally described this histological picture and named it the "wire-loop" lesion. However, we agree with Allen (1955) and Hass (1955) that the fibrinoid thickening of the glomerular basement membrane is more correctly named "membranous glomerulonephritis".

We wish to emphasize that the advanced "wire-loop" lesions seen in patients with florid S.L.E. differ somewhat from the glomerular lesions seen in patients diagnosed as having membranous glomerulonephritis (Ellis Type II; Ellis, 1942). In lupus nephritis, the glomerular thickening was not uniform; fibrinoid changes were common in the glomerular endothelial membrane of lupus nephritis and rare in Ellis Type II glomerulonephritis; patchy hypercellularity was a characteristic feature of lupus nephritis, but was usually not present in the glomeruli of Ellis Type II glomerulonephritis. A comparison of typical examples of these two lesions is shown in Figs 4-A and 5 (overleaf).

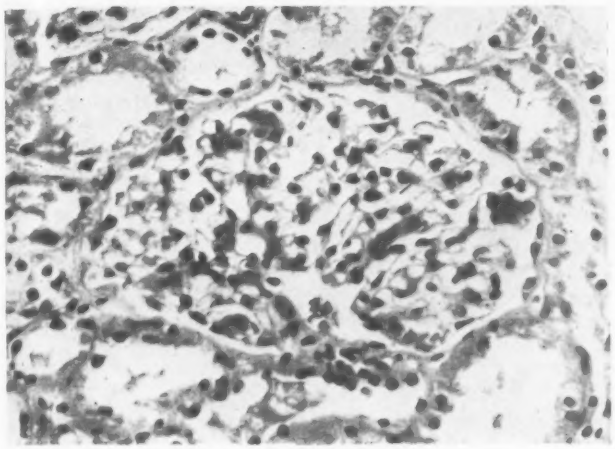


Fig. 1.—Local glomerulitis in lupus nephritis.
Photomicrograph: Haematoxylin and eosin ×285.
A 32-year-old housewife had signs and symptoms of S.L.E. for 18 months before a small number of leucocytes and occasional granular and leucocyte casts were found in the urine. There was no proteinuria, and renal function tests were normal.
A renal biopsy revealed "local glomerulitis".
Note localized areas of hypercellularity, especially in periphery of glomerulus. Mild "fibrinoid" changes in the glomerular basement membrane can be seen within the areas of hypercellularity.

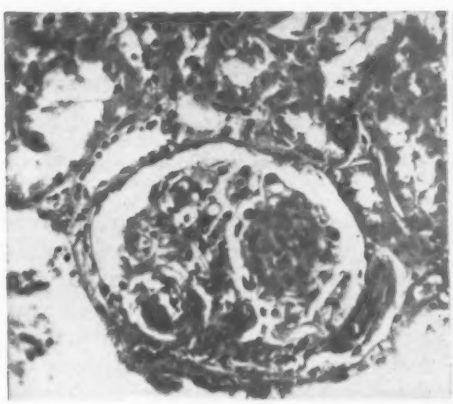


Fig. 2(*a*).—(June, 1954) Severe local glomerulitis simulating focal embolic glomerulonephritis.
Photomicrograph: Haematoxylin and eosin ×165.
A 12-year-old Negro school girl had signs and symptoms of S.L.E.; 11 months after admission to the clinic a trace of protein, numerous leucocytes, and a few casts were found in the urine. Renal function tests were normal. Study of the first renal biopsy (*a*) revealed severe "local glomerulitis". Note large area of hypercellularity with nuclear karyorrhexis within glomerular tuft. Moderate "fibrinoid" changes can be seen within glomerular basement membrane. This lesion simulates the histological picture of focal embolic glomerulonephritis.

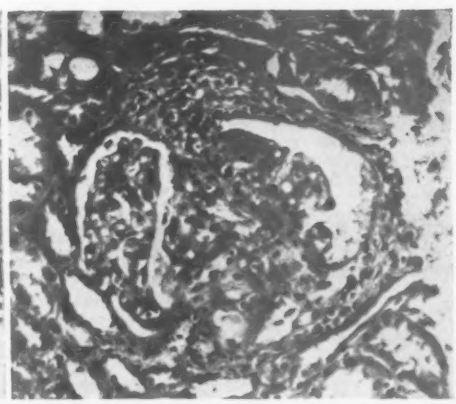
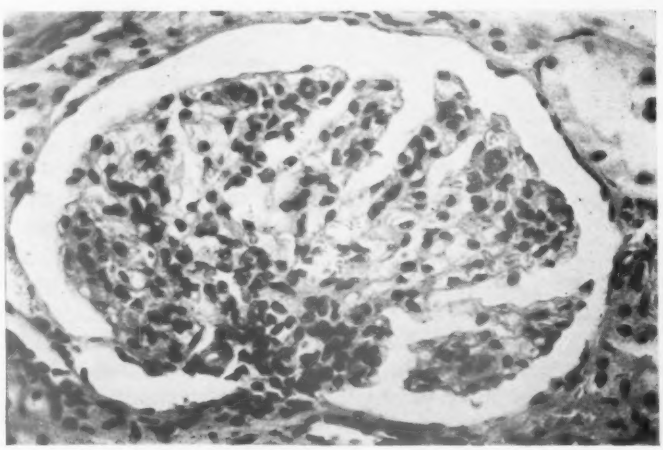


Fig. 2(*b*).—(February, 1955) Local glomerulitis with adhesions.
Photomicrograph: Haematoxylin and eosin ×165.
A second renal biopsy was taken 6 months later when the patient had developed the nephrotic syndrome. Gross proteinuria, doubly refractile bodies, and numerous fatty, hyaline, and granular casts were found in the urine.
Note local hypercellularity in glomerular tuft, irregular "fibrinoid" thickening of glomerular basement membrane, and adhesion between glomerular tuft and Bowman's capsule.

Fig. 3.—General glomerulitis.
Photomicrograph: Haematoxylin and eosin ×280.
A 23-year-old Negro woman was ill with S.L.E. for 2 years. A trace of protein, a few leucocytes, and hyaline casts were found in the urine. Renal biopsy disclosed "general glomerulitis". Note diffuse hypercellularity of glomerular tuft, no significant changes in glomerular basement membrane or in Bowman's capsule.



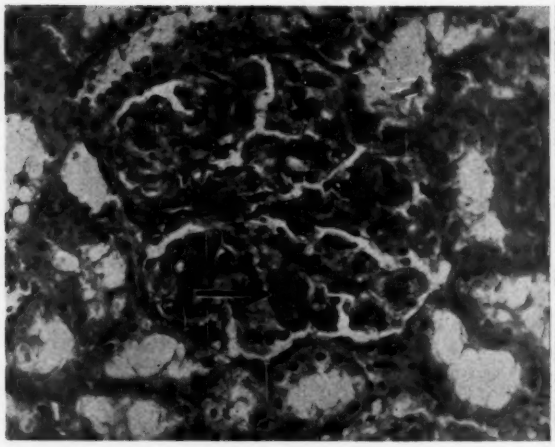


Fig. 4(*a*).—(September, 1954) Local membranous glomerulonephritis ("wire-loop" type).
Photomicrograph: Haematoxylin and eosin ×200.
A 22-year-old Negro woman had had florid S.L.E. for slightly less than 2 years, when gross proteinuria, several leucocytes, and leucocyte and granular casts were found in the urine. Renal functions were markedly impaired. The first renal biopsy disclosed "local membranous glomerulonephritis". Note marked local "fibrinoid" thickening of glomerular basement membrane simulating wire loops. The glomerulus is lobulated and ischaemic. General mild hypercellularity can be seen.

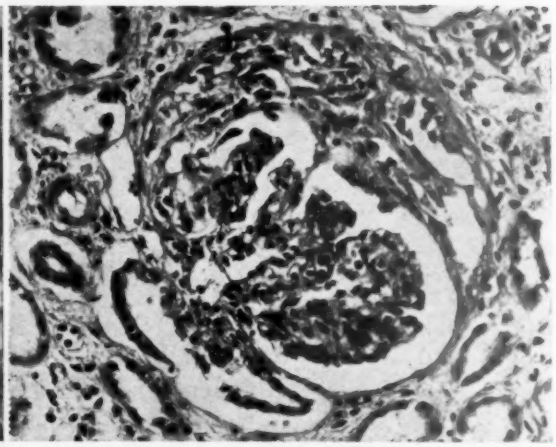


Fig. 4(*b*).—(November, 1954) Subacute glomerulonephritis.
Photomicrograph: Haematoxylin and eosin ×200.
Two months later the patient became uraemic. Her blood pressure increased to 180/112 mm. Hg, and she died of pulmonary oedema and renal failure. At autopsy the kidneys were large, swollen, and pale. Histological examination revealed typical subacute glomerulonephritis.
Note large fibro-epithelial crescent in Bowman's space. The glomerular tuft is lobulated, contracted, and moderately hypercellular. An area of local hypercellularity can also be seen at the periphery of the glomerular tuft.

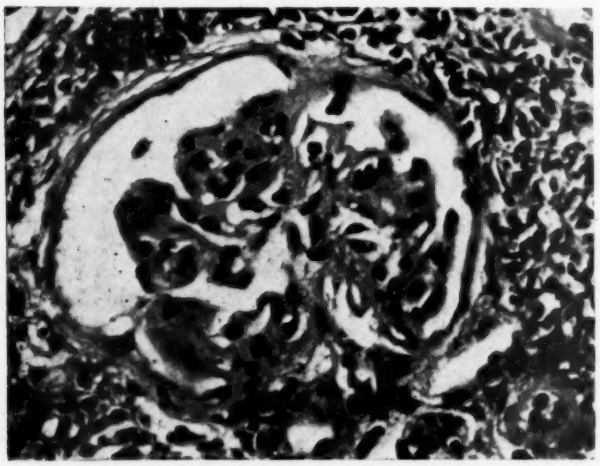


Fig. 5.—Chronic membranous glomerulonephritis (Ellis Type II).
Photomicrograph: Haematoxylin and eosin ×275.
This typical example of chronic membranous glomerulonephritis (Ellis Type II) should be compared with the local membranous glomerulonephritis of lupus nephritis (see Text).
A 44-year-old taxicab driver developed the nephrotic syndrome in 1953. Detailed clinical and laboratory studies indicated Ellis Type II membranous glomerulonephritis. Note marked, *diffuse* thickening of glomerular basement membrane which is dense. The homogeneous hyaline thickening of the membrane differs from the granular clotted appearance of "fibrinoid" thickening.

Subacute glomerulonephritis was commonly found in patients with lupus nephritis. These lesions developed as early as 2 months after the "wire-loop" stage of lupus nephritis (Fig. 4-B) and were usually found in biopsy material from patients with S.L.E. who had the nephrotic syndrome.

This stage of lupus nephritis was characterized by ischaemic, moderately hypercellular glomeruli in which "wire-loop" lesions might or might not be detected. In addition, fibro-epithelial crescents of Bowman's capsule were seen in many glomeruli, which were compressed and reduced in size. Usually the convoluted tubules were moderately degenerated. Within the interstitial tissue, moderate to severe oedema was noted, and this was usually associated with the presence of chronic inflammatory cells. In three patients, the lesions of chronic glomerulonephritis (Fig. 6-B) were found in the renal biopsy tissue. These lesions and those described above under "subacute glomerulonephritis" were typical of those seen in Ellis Type I glomerulonephritis (Fig. 6-A). Nevertheless, we have observed the progression of "wire-loop" lesions (local membranous glomerulonephritic stage of lupus nephritis) to typical subacute glomerulonephritis (Fig. 6-A) which could not be distinguished from the lesions of the Ellis Type I.

Thus far, renal insufficiency has been the cause of death in all the six patients from our biopsy series who have died; and in each of these patients the kidneys were severely damaged, either with local membranous glomerulonephritis or with typical lesions of subacute glomerulonephritis. It has been stated that kidneys in patients with lupus nephritis are normal or enlarged (Allen, 1951; Baggenstoss, 1952), and in general we agree with this statement. In 35 autopsied cases of S.L.E. which we have

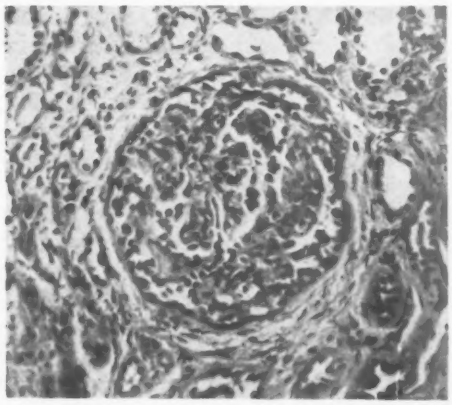


Fig. 6(*a*).—Subacute glomerulonephritis (lupus nephritis).
Photomicrograph: Haematoxylin and eosin ×165.
A 21-year-old youth was ill with S.L.E. for one year before he developed the nephrotic syndrome. The first renal biopsy was taken 4 months after the onset of oedema when renal function was moderately impaired. Large kidneys were seen on *x* ray. The histological diagnosis was the subacute glomerulonephritic stage of lupus nephritis. Note diffuse hypercellularity of glomerular tufts which are adherent to Bowman's capsule in many areas, marked epithelial cell proliferation of Bowman's capsule, tubular atrophy, and interstitial fibrosis can be seen.

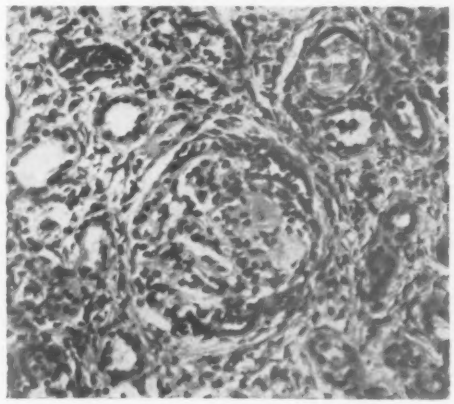


Fig. 6(*b*).—Chronic glomerulonephritis (lupus nephritis).
Photomicrograph: Haematoxylin and eosin ×165.
Eight months later the patient had developed hypertension (blood pressure: 170/115 mm. Hg) and his renal function was markedly impaired. Small kidneys were seen on *x* ray. The histological diagnosis was the chronic glomerulonephritic stage of lupus nephritis. Note partial hyalinization of glomerular tuft and contraction of glomerulus. The tubular atrophy and interstitial fibrosis are more severe than in (*a*).

studied, not a single "contracted kidney" was found.

However, in one of our patients, presently ill with lupus nephritis and with histological evidence of chronic glomerulonephritis on biopsy, the kidneys were found to be small on *x* ray of the abdomen.

"Wire-loop" lesions and haematoxylin bodies were not commonly seen. Typical "wire-loop" lesions were found in only four of 61 biopsies. In reviewing renal tissue from 35 autopsied cases of S.L.E., none of whom had been biopsied, "wire-loop" lesions were found in nine patients. In view of the discrepancy between our biopsy data and the finding of Klemperer and others (1941) of a high incidence of "wire-loop" lesions in S.L.E., one can speculate that "wire-loop" lesions exist only as a stage of renal involvement in this disease, appearing between the early and the late manifestations of lupus nephritis. If this speculation were true, it would mean that "wire-loop" lesions were transitory and short-lived. Another explanation is that "wire-looping" may be an expression of the severity of the fibrinoid reaction which is so characteristic of S.L.E. In the pre-steroid therapy days, patients with S.L.E. died in "lupus crisis", and massive fibrinoid changes commonly occurred (Keith, 1940; Muehrcke and others, 1955c). Nowadays, steroid therapy appears to suppress the basic disease reaction which produces or results in severe fibrinoid changes. Unfortunately, steroid therapy does not prevent the progression of local glomerulitis to the general glomerulitis stage of lupus nephritis and further progression of this latter lesion to chronic glomerulonephritis. We are certain that local glomerulitis is not the result of cortisone therapy, because this lesion was commonly found in the kidneys of patients with S.L.E. before ACTH or steroid therapy was introduced (Stickney and Keith, 1940). Whether steroid or ACTH therapy aggravates lupus nephritis in man once the lesion develops in the kidney is not known. This is a clinical point for further investigation, as animal studies indicate that administration of ACTH or steroids may produce or aggravate experimentally-induced glomerulonephritis (Teilum and others, 1951; Bloodworth and Hamwi, 1955).

Pseudo-Nephrotic Syndrome and Nephrotic Syndrome associated in Lupus Nephritis

In our series of 32 patients with lupus nephritis, five developed the nephrotic syndrome. The clinical and laboratory findings in these patients fulfilled the criteria set forth by Leiter (1931). All five patients had had a facial rash early in their disease, but none of them had the rash at the height of the nephrotic syndrome This change has been commented on previously (Brenner and others, 1948). Three other patients ill with lupus nephritis were admitted with the clinical features of the nephrotic syndrome; these were unusual because the serum levels of cholesterol and cholinesterase were extremely low, despite the finding of doubly refractile bodies in the urine. Their clinical course was also

unusual, as they developed rapid progressive renal failure and died within 2 to 4 months after the oedema first appeared. Histological findings were also different from those seen in the group of five patients with typical nephrotic syndrome, as hyaline thrombi, marked fibrinoid changes, and severe inflammatory reaction were observed (Fig. 7). Because of the unusual clinical, laboratory, and histological features presented by these three patients, we have grouped them together as cases of the "pseudo-nephrotic syndrome".

Correlation between Urine Analysis, Renal Function and Renal Histology

Preliminary study of our data shows that a correlation exists between urine analysis, tests of renal function, and histological findings in the kidney. With the earliest lesion—local glomerulitis—the urine often mimicked that found in pyelonephritis; that is, the specific gravity was normal; one plus proteinuria was present, and the urinary sediment contained many white blood cells, a few red blood cells, and a few casts. The P.S.P., urea clearance, and blood pressure were within normal limits.

By the time subacute glomerulonephritis developed the urine specific gravity had fallen (ranging between 1·017 and 1·022), massive proteinuria was present, and numerous casts were seen, including fatty casts and doubly refractile bodies. The 15-min. P.S.P. excretion test ranged between 13 and 22 per cent., and the urea clearance also fell. The blood pressure was normal and did not rise until chronic glomerulonephritis developed. In this late stage of lupus nephritis the specific gravity was fixed, four plus proteinuria was noted, and few cellular elements were seen on microscopic examination. However, some broad casts were found. Renal function was severely depressed at this stage of the disease.

Summary

The histological evolution of lupus nephritis was studied in 32 patients with systemic lupus erythematosus by percutaneous needle biopsy, and 22 patients had serial renal biopsies. Histological data were correlated with the changing clinical status, laboratory data, and renal function tests.

The earliest glomerular involvement was a local glomerulitis characterized by local hypercellularity and occasionally by fibrinoid changes. Glomerular

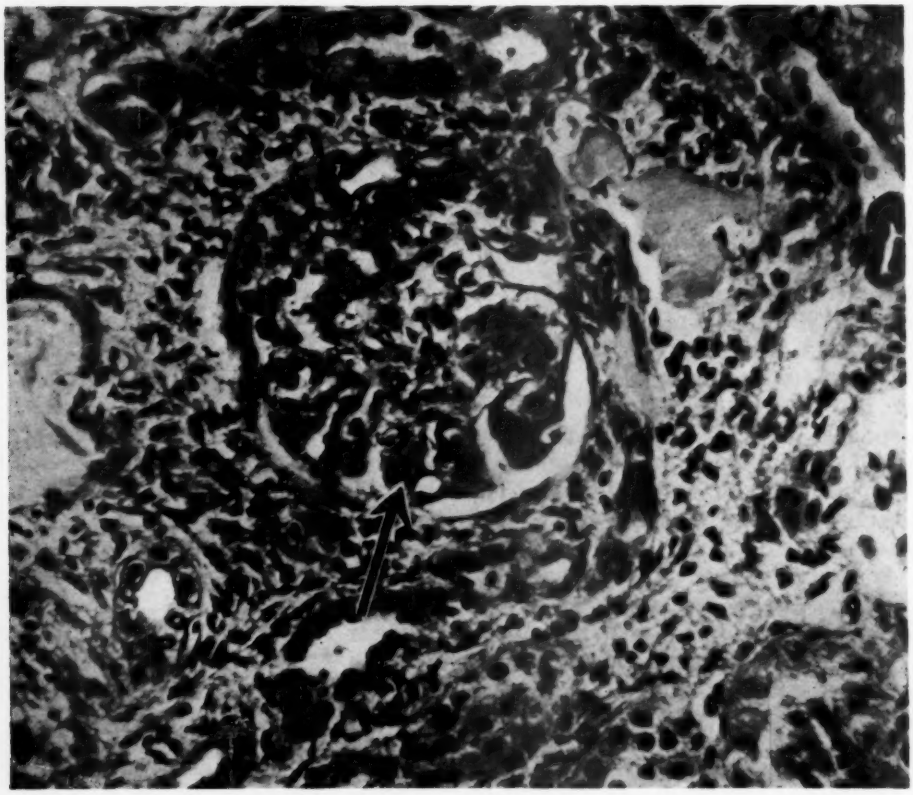


Fig. 7.—Localized membranous glomerulonephritis ("pseudo-nephrotic" stage of lupus nephritis).
Photomicrograph: Haematoxylin and eosin ×330.
An 18-year-old girl developed signs and symptoms of S.L.E. in July, 1954. One month later, oedema of the legs, face, and eyelids appeared. Gross proteinuria and numerous fatty, hyaline, and cellular casts were found in the urine.
In October, 1954, she developed uraemia and hypertension (blood pressure: 160/110 mm. Hg); the oedema persisted. The levels of serum cholesterol and cholinesterase were reduced. The patient died as a result of renal failure soon after the biopsy was taken.
The histological diagnosis was the local membranous glomerulonephritic stage of lupus nephritis. Note irregular "fibrinoid" thickening of glomerular basement membrane which is very broad in some areas. The glomerulus is ischaemic but not hypercellular. A hyaline thrombus is seen within one capillary lumen (arrow). The interstitial tissue is markedly oedematous and contains chronic inflammatory cells.

lesions progressed from local glomerulitis, through general glomerulitis, to subacute glomerulonephritis. In the biopsy material, "wire-loop" lesions were rarely seen and appeared to represent a transitory stage in the development of lupus nephritis.

There were two distinct groups of oedematous patients with lupus nephritis: one had the clinical and laboratory features of the nephrotic syndrome; the second had a pseudo-nephrotic syndrome associated with low serum levels of cholesterol and cholinesterase. Their illness progressed rapidly to its termination, and they died in renal failure a few months after oedema appeared.

Urine analysis correlated with renal pathology. White blood cells and white blood cell casts were found with local glomerulitis. Mild proteinuria was associated with general glomerulitis. Impairment of renal function was observed with subacute glomerulonephritis. Hypertension and a fixed specific gravity accompanied chronic glomerulonephritis.

This study demonstrated the value of correlating the progression of histological changes with the concomitant clinical and laboratory data in observing the natural history of a disease.

REFERENCES

Allen, A. C. (1951). "The Kidney. Medical and Surgical Diseases", p. 170. Grune and Stratton, New York.
—— (1955). *Amer. J. Med.*, **18**, 277.
Baehr, G., Klemperer, P., and Schifrin, A. (1935). *Trans. Ass. Amer. Phys.*, **50**, 139.
Baggenstoss, A. H. (1952). *Proc. Mayo Clin.*, **27**, 412.
Bloodworth, J. M. B., Jr., and Hamwi, G. J. (1955). *Amer. J. Path.*, **31**, 167.
Brenner, J. J., Leff, W. A., and Hochstein, E. (1948). *Amer. J. Med.*, **5**, 288.
Ellis, A. (1942). *Lancet*, **1**, 1.
Hargraves, M. M., Richmond, H., and Morton, R. (1948). *Proc. Mayo Clin.*, **23**, 25.
Hass, G. M. (1955). Personal communication.
Kark, R. M., and Muehrcke, R. C. (1954). *Lancet*, **1**, 1047.
Keith, N. M. (1940). *Proc. Mayo Clin.*, **15**, 682.
Klemperer, P., Pollack, A. D., and Baehr, G. (1941). *Arch. Path. (Chicago)*, **32**, 569.
Leiter, L. (1931). *Medicine (Baltimore)*, **10**, 135.
Muehrcke, R. C., Kark, R. M., and Pirani, C. L. (1955a). *J. Urol.*, **74**, 267.
——, ——, ——, and Pollak, V. E. (1955b). *Clin. Res. Proc.*, **3**, 139.
——, Pirani, C. L., and Kark, R. M. (1955c). Personal observations.
Pirani, C. L., Muehrcke, R. C., and Kark, R. M. (1954). *Proc. Instit. Med. Chi.*, **20**, 170.
Stickney, J. M., and Keith, N. M. (1940). *Arch. intern. Med.*, **66**, 643.
Teilum, G., Engbaek, H. C., Harboe, N., and Simonsen, M. A. (1951). *J. clin. Path.*, **4**, 301.

Evolution clinique et histologique de la néphrite compliquant le lupus érythémateux

RÉSUMÉ

On étudia l'évolution histologique de la néphrite chez 32 malades atteints de lupus érythémateux généralisé à l'aide de la ponction percutanée et chez 22 d'entre eux des biopsies rénales en série. Les données histologiques furent considérées à la lumière de l'évolution clinique, des résultats de laboratoire et des résultats des épreuves de la fonction rénale.

La première atteinte glomérulaire fut une glomérulite locale caractérisée par l'hypercellularité locale et, quelquefois, par des altérations fibrinoïdes. De là, la glomérulite tendait à se généraliser, évoluant vers la glomérulonéphrite subaiguë. Dans le matériel prélevé on ne vit que rarement des lésions à "l'anse filiforme" (*wire-loop*) qui semblent représenter un stade transitoire de l'évolution de la néphrite lupique.

Parmi les malades oedémateux atteints de néphrite lupique il y avait deux groupes distincts: l'un présentait des caractères cliniques et de laboratoire du syndrome néphrotique; chez l'autre le tableau du syndrome pseudo-néphrotique était accompagné d'un taux sérique bas de cholestérol et de cholinestérase. Leur maladie évoluait rapidement vers la mort d'insuffisance rénale peu de mois après le début de l'oedème.

L'état de l'urine correspondait aux lésions du rein. Au stade de glomérulite locale on trouvait des leucocytes et des cylindres et au cours de la glomérulite généralisée un peu d'albumine. Une amélioration de la fonction rénale s'observait au cours de la glomérulonéphrite subaiguë. La glomérulonéphrite chronique s'accompagnait d'hypertension et de densité constante.

Ce travail montre la valeur de l'étude comparée des altérations histologiques progressives et des données cliniques et de laboratoire concomitantes quand on observe l'histoire naturelle d'une maladie.

Evolución clinica e histológica de la nefritis luposa

SUMARIO

Se estudió la evolución histológica de la nefritis en 32 enfermos con lupus eritematoso generalizado por medio de biopsias por punción percutánea y en 22 de ellos por medio de biopsias renales seriadas. Los datos histológicos fueron considerados en relación con las alteraciones clínicas, de laboratorio y de la función renal.

El compromiso glomerular iniciaba con una glomerulitis local caracterizada por una hipercelularidad local y, a veces, con alteraciones fibrinoides. Luego, la glomerulitis se generalizaba acabando con una glomerulonefritis subaguda. En los fragmentos de biopsia se vieron pocas lesiones del tipo "asa filiforme" (*wire-loop*); esas parecen representar una etapa transitoria en la evolución de la nefritis luposa.

Hubo dos grupos distintos de enfermos edematosos con nefritis luposa: uno con los rasgos clínicos y de laboratorio del síndrome nefrótico y el otro con el síndrome seudo-nefrótico asociado con cifras séricas bajas de colesterol y de colinesterasa. La enfermedad de éstos progresaba rapidamente hacia la muerte poquísimos meses después del comienzo del edema.

Los hallazgos en la orina correspondían a las lesiones renales. Leucocitos y cilindros aparecían con la glomerulitis local y un poco de albumina con la glomerulitis generalizada. Una mejoría de la función renal se observaba en el curso de la glomerulonefritis subaguda. La glomerulonefritis crónica se acompañaba de hipertensión y de densidad fija.

Este estudio demuestra el valor de la correlación del progreso de las alteraciones histológicas con los datos clínicos y de laboratorio concomitantes al observar la historia natural de una enfermedad.

Ann. rheum. Dis. (1955), **14**, 378.

COMPARISON OF RHEUMATOID (ANKYLOSING) SPONDYLITIS AND CRIPPLING FLUOROSIS*†

BY

CHARLES LEROY STEINBERG

Rochester General Hospital

AND

DWIGHT E. GARDNER, FRANK A. SMITH, AND HAROLD C. HODGE

Division of Pharmacology and Toxicology
Department of Radiation Biology
University of Rochester School of Medicine and Dentistry
Rochester, New York

(RECEIVED FOR PUBLICATION JULY 5, 1955)

Crippling fluorosis and rheumatoid (ankylosing) spondylitis present a confusing similarity; both are characterized in their advanced stages by a "poker-back" spine with calcification of the ligaments of the spinal column (Fig. 1). Rheumatic pains of various degree are common in the early stages of both diseases.

One of us (C.L.S.), noting the similarity between

* This paper is based in part on work performed under contract with the U.S. Atomic Energy Commission at the University of Rochester Atomic Energy Project, Rochester, New York.

† Presented but not read at the Annual General Meeting of the American Rheumatism Association, 1955. See p. 443 of this issue.

A B C D

Fig. 1.—"Poker Back", comparison of limitation of motion and characteristic stance in (A and B) rheumatoid spondylitis, and (C and D) crippling fluorosis. C and D are reproduced with the permission of the publishers from Roholm (1937, opp. p. 145, Figs 33*b* and *c*).

these conditions, suggested the importance of presenting a comparison of the two conditions. Recent public health undertakings in the United States, designed to reduce the incidence of dental caries by adding fluoride to the communal water supply, have increased the importance of this investigation. It would be unfortunate if these undertakings were erroneously accused of producing serious bone changes through the inadvertent diagnosis of rheumatoid (ankylosing) spondylitis as crippling fluorosis.

Rheumatoid (Ankylosing) Spondylitis

This condition is usually considered by most rheumatologists to be a variant of rheumatoid arthritis. It usually affects males in contradistinction to the usual variety of rheumatoid arthritis which generally affects females. It usually begins in youth, is characterized by exacerbations and remissions of back pain, and may or may not be associated with the sciatic syndrome. As the disease progresses a gradual stiffening of the back occurs, eventually resulting in a "poker-back" spine. Expansion of the chest on inspiration becomes diminished and finally nil as ankylosis of the costovertebral joint occurs. The radiographic picture is pathognomonic. The first changes usually occur in the sacro-iliac joints. The joint surface becomes irregular; there is progressive increase in density in the contiguous bone surfaces of this joint. Eventually the sacro-iliac joints may be completely obliterated by bony ankylosis. At this particular point the area in which the joint has been erased is usually very dense; the surrounding bone area may show a decrease in density. The trabeculae become more prominent. Calcification occurs in the anterior and longitudinal ligaments of the vertebral column. However, there is no calcification in the sacral tuberous and other ligaments of the pelvis, nor are the fasciae involved. Primary fibrous and subsequent bony ankyloses of the apophyseal joints result in a rigid spinal column ("poker-back" spine). Approximately 25 per cent. of these patients have involvement of the peripheral joints with a clinical pattern not unlike rheumatoid arthritis. The sedimentation rate is elevated in a majority of the cases.

Crippling Fluorosis

Crippling fluorosis is a specific form of skeletal disease which follows the absorption of excessive amounts of fluoride for prolonged periods of time. Osteosclerosis and exostoses are the outstanding findings; mottled dental enamel may be seen if the period of *absorption* includes the first 8 years of life when the enamel of the permanent teeth is being formed. In some instances areas of osteoporosis also are seen. As the disease progresses all bones eventually become sclerotic; there seems to be a predilection, however, for flat bones, such as those of the pelvis and jaw, and especially the lumbar vertebral system to show the first detectable changes (Felson, 1955). In severe cases, exostoses become evident on the long bones, and on the lower edges of the vertebrae. Eventually the vertebrae fuse together, the spinal ligaments become calcified at their points of attachment, and the typical rigid spinal column ensues (Figs 2, 3, and 4, overleaf). Crippling fluorosis of industrial origin was fully described by Roholm (1937) in his investigation of the disease in Danish cryolite workers. The condition is also endemic in various parts of the world, India, China, Argentina, and South Africa, where water supplies contain 2-16 parts per million of fluoride. From data presented by McClure (1943), fluoride doses probably must be greater than 0·1 mg./kg./day during the first 8 years of life to produce mottled enamel. It has been estimated that the daily consumption of 0·3-1·0 mg. fluoride per kg. body weight for a period of 10-20 years will result in crippling fluorosis (Roholm, 1937; Hodge and Smith, 1954).

Present Investigation

To our knowledge no one has reported the fluoride content in the skeletal tissues of an individual suffering from rheumatoid spondylitis. It was our unusual fortune recently to study such a case; this man who had had the disease for a period of 10 years died suddenly of a subarachnoid haemorrhage.

Case History

A white male aged 40 years, first seen on September 22, 1948, gave a 10-year history of low back pain with progressive spinal stiffening, and increased pain and stiffness of the hips. He had lived in Rochester, N.Y., all his life, and never had left the area for any period longer than a few days. The fluoride content of the tap water by analyses in the period 1945 to 1952 was low, about 0·06 parts per million; presumably this is a reliable estimate of the fluoride content of Rochester's water supply during the man's life time.

The physical examination revealed no dental mottling. He lacked 15° abduction in both shoulders; there was no chest expansion on deep inspiration, which was thought to be indicative of ankylosis of the costovertebral joints. He was unable to abduct either hip, and a 45° flexion deformity was present in both. His entire spine was rigid.

Laboratory Findings.—September 22, 1948:

Antistreptolysin titre, 83 units; red blood cells, 4,530,000; haemoglobin, 12 g. per cent.; white blood cells, 13,600.

Fig. 2.—Moderately advanced crippling fluorosis in male, lumbo-sacral area. Note increased bone density (sclerosis) and loss of normal trabecular pattern.

Fig. 3.—Advanced crippling fluorosis, lumbo-sacral area. Note complete loss of bone trabecular pattern and "marble" type bone due to increased bone sclerosis. Moderate calcification of ligaments.

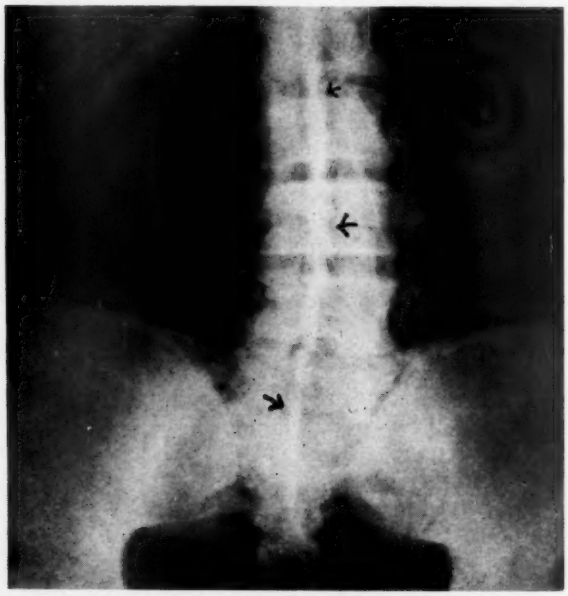


Fig. 4.—Advanced crippling fluorosis, lumbo-sacral area. Advanced calcification of ligaments (arrows). Marked increase in bone sclerosis appears to "obliterate" normal sacro-iliac joints.

Differential Blood Count: stabs, 2 per unit; segmented neutrophils, 78 per cent.; lymphocytes, 10 per cent.; eosinophils, 3 per cent.; monocytes, 7 per unit; blood uric acid, 1·6; serum calcium, 10·4; serum phosphorus, 3·9 mg. per cent.; erythrocyte sedimentation rate, 35 mm./hr (Wintrobe-Landsberg). Subsequent sedimentation rates varied between 21 and 39 mm. Bone marrow fat 3, plasma 48, erythromyeloid layer 9, haematocrit 40 vol. per cent. The marrow showed no abnormalities.

Radiographs (September 22, 1948).—Anterior-posterior stereo and lateral films of the cervical spine (Fig. 5, opposite) showed calcification in the anterior vertebral ligaments. In addition there was evidence of bony sclerosis or ligamentous calcification along the posterior portion of the articular facet in the lower cervical region. The cervical bodies and intervertebral spaces appeared to be normal.

In the thoracic spine moderate scoliosis was seen with a major curve at the lumbo-dorsal region with the convexity on the left side. There was evidence of mild osteoporosis involving the thoracic segments, but no other definite changes.

The lumbar spine and pelvis (Figs 6 and 7, opposite) showed advanced ligamentous calcification along the anterior borders of the lower lumbar vertebral bodies

Fig. 5.—Rheumatoid spondylitis, lateral view of cervical spine. Note bony ankylosis of apophyseal joints.

and suspected calcification in the posterior ligaments. There was no evidence of bony sclerosis in the sacro-iliac region on either side, but there was evidence of destructive arthritic change involving both hips with irregularity of the femoral head and acetabulum. Ligamentous calcification was seen inferiorly about both hip joints.

Treatment.—A left cup arthroplasty was done on January 14, 1949. There was slight irregular new bone formation in an area where the cartilage was denuded. The periosteum was thickened irregularly.

A right cup arthroplasty was done on May 9, 1949. The microscopic sections revealed a markedly proliferative synovial tissue with foci of inflammatory cells beneath the mesothelium. The bone tissue was essentially normal.

Death.—On May 13, 1952, the patient died suddenly of a subarachnoid haemorrhage.

Autopsy.—Portions of the ribs, vertebrae, and sacrum and ilium immediately adjacent to the sacro-iliac joint were taken for fluoride analysis. The soft tissue adhering to each of the specimens and marrow from the two rib specimens were analysed separately. The vertebral sample was separated into the spongy and dense portions, (Fig. 8, overleaf). The soft tissues were analysed according to the method described by Smith and Gardner (1951) for blood fluoride. After ashing the hard tissues, fluoride was separated by the perchloric acid distillation of Willard and Winter (1933); fluoride in the distillate was determined by salt-acid thorium titration (Smith and Gardner, 1950). The data obtained are shown in Table I (overleaf).

Fig. 6.—Rheumatoid spondylitis, lateral view of lumbo-sacral area. Note calcification of anterior spinal ligament.

Fig. 7.—Rheumatoid spondylitis, anterior-posterior view of pelvis. Note ankylosis of sacro-iliac joints and increased trabeculation of bone.

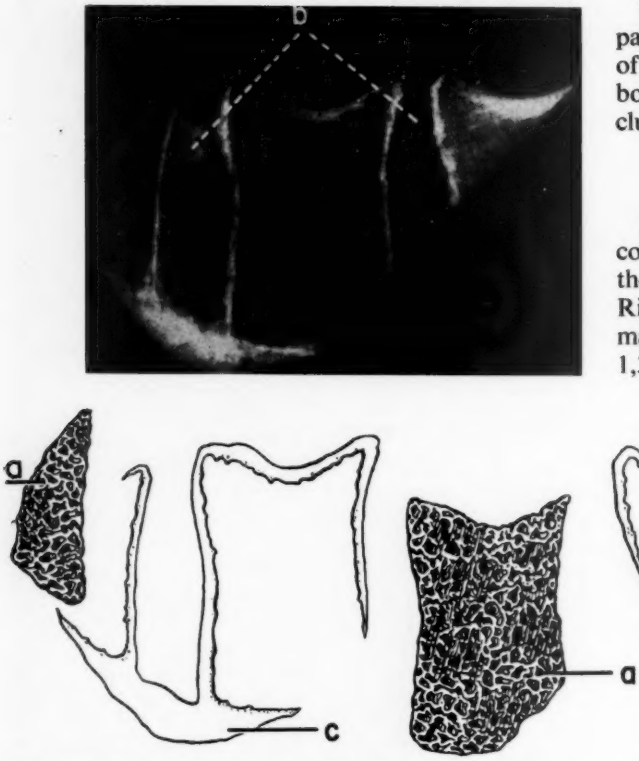


Fig. 8.—Separation of vertebral sample from a case of rheumatoid spondylitis for fluoride analysis: (*a*) spongy portion, 410 p.p.m. fluoride in ash; (*b*) soft tissue, 17 p.p.m. fluoride fresh wt.; (*c*) dense portion, 310 p.p.m. fluoride in ash.

TABLE I

FLUORIDE CONCENTRATIONS IN TISSUES

Site of Tissue		Fluoride (parts per million)	
		in Ash	in Fresh Tissue
Rheumatoid Spondylitis Patient	Ilium	320	
	Sacrum	310	
	Soft tissue between sacrum and ilium		9
	Smaller rib including marrow	420	
	Smaller rib without marrow	440	
	Smaller rib marrow		17
	Soft tissue around smaller rib		10
	Larger rib including marrow	420	
	Larger rib without marrow	440	
	Larger rib marrow		10
	Soft tissue around larger rib		9
	Vertebra, spongy portion	410	17
	Soft tissue from vertebra		
	Vertebra, dense portion	310	
Controls*	Rib	405-1,215	
	Soft tissue around rib		9-21
	Rib marrow		26
	Vertebra	440-1,320	
	Soft tissue round vertebra		7-20

* Smith, Gardner, and Hodge, 1955.

There were no known opportunities for this patient to have been exposed to excessive amounts of fluoride. Nevertheless, the fluoride content of bone samples, which are shown to be normal, conclusively rule out fluorosis as a factor in the disease.

Discussion

Fluoride is a normal trace constituent of bone, the contents depending on the fluoride intake, the age of the individual, and probably on other factors. Rib and vertebral specimens from 40 to 50-year-old male residents of the Rochester area contained 400 to 1,300 p.p.m. fluoride in the ash (Smith, Gardner, and Hodge, 1955). Martin (1948) has reported similar fluoride concentrations in dry defatted samples from the crest of the ilium obtained in Evanston, Illinois, prior to water fluoridation; using the data of Robinson (1952) for fat content, these adult bones were calculated to contain 470 to 1,430 p.p.m. fluoride in the ash.

The data in Table I show that the tissues of the ribs of our patient contained low but normal amounts of fluoride, whereas the vertebra contained slightly less fluoride than had been found in control patients of the same age (Smith, Gardner, and Hodge, 1953). The ilium also contained slightly less fluoride than Martin (1948) reported for a series of nine samples of the iliac crest.

Soft tissues contain normally only traces of fluoride; the finding that fluoride concentrations in the soft tissues and marrow (9 to 17 p.p.m.) were much lower than those found for the hard tissues was expected. Concentrations found for comparable tissues from five patients without rheumatoid spondylitis, 14 to 86 years of age, averaged 9 to 26 p.p.m.

The data obtained in this study indicate that the increased osteosclerosis encountered in rheumatoid spondylitis is not associated with increased skeletal

TABLE II

FLUORIDE CONCENTRATIONS IN BONE

Site	Fluoride (parts per million)		
	Normal*	Rheumatoid Spondylitis	Crippling Fluorosis†
Rib ..	405-1,215	420-440	9,900-11,200
Vertebra ..	440-1,320	310-410	9,300-13,100

* Smith and others (1953).
† Roholm (1937), p. 193.

TABLE III

COMPARISON OF RHEUMATOID SPONDYLITIS, CRIPPLING FLUOROSIS, AND METASTATIC CARCINOMA

Condition	Rheumatoid Spondylitis	Crippling Fluorosis	Metastatic Carcinoma (Prostate and Breast)
(1)	Increase in trabecular pattern upon roentgenological examination	Coarse and blurred trabeculae, diffuse increased density of bone on roentgenological examination	Localized areas of increased bone density
(2)	Increased density of sacro-iliac joints and increased density of ilium and sacrum with progressive disease	Vertebral system and pelvis affected first and most severely; later extended to ribs and extremities. All bones are affected, particularly cancellous bones. Exostoses on long bones	Pelvic area and lumbar spine affected first. Areas of increased bone density usually discrete, but occasionally diffuse. No cortical thickening
(3)	Universal occurrence	Endemic where water supplies contain excessive amounts of fluoride. Formerly seen in workers handling fluoride-containing compounds	Universal occurrence
(4)	Calcification of ligaments limited to anterior and lateral spinal column	Excessive calcification of tendons, ligaments, fasciae	No ligamentous calcification
(5)	Peripheral joints swollen in 25 per cent. of cases	Bones of extremities thickened	No peripheral joint involvement
(6)	No mottled enamel	Mottled enamel may be present if fluoride exposure excessive during period of formation of enamel of permanent teeth	No mottled enamel
(7)*	No increased urinary fluoride excretion	Urinary excretion of fluoride increased	No increase in urinary fluoride excretion
(8)†	Skeletal fluoride concentration not increased	Increase in skeletal fluoride concentration	No increase in skeletal fluoride concentration
(9)	No increase in serum phosphatase	No increase in serum phosphatase	Increase in serum alkaline, acid phosphatase, or both

* When the fluoride concentration in the urine is consistently less than 5 mg./l., no roentgenographically demonstrable osteosclerosis develops (Irwin, 1954).

† Normal concentration of fluoride in human bone (Smith, Gardner, and Hodge, 1955, unpublished data):

Sex	Site	Age	P.p.m.
Male	Rib	10	300
		90	1,480
	Vertebrae	10	380
		90	1,520
Female	Rib	10	240
		90	1,200
	Vertebrae	10	320
		90	1,260

deposition of fluoride. Indeed, the skeletal fluoride concentrations were near or less than the normal limits previously established. Fluoride cannot be held responsible for the bony changes in rheumatoid spondylitis. Roholm (1937) has shown that the skeletal tissues of patients disabled with fluorosis contain relatively high concentrations of fluoride. Representative data for rib and vertebra are shown in Table II. Wolff and Bauer (1938) reported greatly decreased fluoride concentrations in occipital, parietal, and frontal bones in a series of six cases of Paget's disease (osteitis deformans).

A comparison of rheumatoid spondylitis, crippling fluorosis, and metastatic carcinoma is presented in Table III. The data on metastatic carcinoma are included because the increased *x*-ray density of certain lumbar vertebrae has presented a problem in differential diagnosis.

Summary

(1) Fluoride concentrations were determined for autopsy samples of rib, sacrum, ilium, vertebra, adhering soft tissue, and rib marrow from a patient suffering from rheumatoid (ankylosing) spondylitis of 10 years' duration. The fluoride concentrations were not increased above normal levels. In this case, the increased bone density seen in this disease was not the result of increased skeletal fluoride deposition.

(2) A tabular comparison of rheumatoid spondylitis, crippling fluorosis, and metastatic carcinoma is presented.

Dr. Robert A. Robinson, formerly of the Division of Orthopaedic Surgery, of the University of Rochester School of Medicine and Dentistry, gave us a number of valuable suggestions and assisted in preparing the samples of sacrum and ilium for analysis. The Department of Medical Photography, Rochester General Hospital, prepared Figs 5-7. Mr. Leon Schwartz of the Photo-

graphy Section, University of Rochester Atomic Energy Project, prepared the diagram Fig. 8. Mr. Fred Brandlin, formerly of the Industrial Hygiene Section, University of Rochester Atomic Energy Project, prepared the *x*-ray shown in Fig. 8.

REFERENCES

Felson, B. (1955). Personal communication.
Hodge, H. C., and Smith, F. A. (1954). "Some Public Health Aspects of Water Fluoridation", *in* "Fluoridation as a Public Health Measure", ed. J. H. Shaw, p. 79. Amer. Assoc. Advance. Sci., Washington, D.C.
Irwin, D. (1954). Personal communication.
Martin, D. J. (1948). *J. dent. Res.*, **27**, 27.
McClure, F. J. (1943). *Amer. J. Dis. Child.*, **66**, 362.
Robinson, R. A. (1952). *J. Bone Jt Surg.*, **34-A**, 389.
Roholm, K. (1937). "Fluorine Intoxication", p. 121. Nyt Nordisk Forlag, Busck, Copenhagen; Lewis, London.
Smith, F. A., and Gardner, D. E. (1950). *Arch. Biochem.*, **29**, 311.
—— —— (1951). *J. dent. Res.*, **30**, 182.
—— ——, and Hodge, H. C. (1953). *Fed. Proc.*, **12**, 368.
—— —— —— (1955). Unpublished observations.
Willard, H. H., and Winter, O. B. (1933). *Industr. Engng Chem., Anal. Ed.*, **5**, 7.
Wolff, W. A., and Bauer, J. T. (1938). *Bull. Ayer clin. Lab.*, 3, 209.

Comparaison de la spondylite rhumatismale et de la fluorose mutilante

RÉSUMÉ

(1) On a determiné le taux de fluor dans les pièces d'autopsie provenant des côtes, du sacrum, de l'os iliaque, des vertèbres, des tissus mous adhérants et de la moelle costale d'un sujet ayant suffert de spondylite rhumatisante pendant dix ans. Le taux de fluor n'était pas au dessus de la normale. Dans ce cas donc la condensation osseuse habituelle dans cette maladie ne pouvait pas être attribuée à l'augmentation des dépôts fluorés du système locomoteur.

(2) On présente des tableaux comparés de spondylite rhumatismale, de fluorose mutilante et de carcinome métastasique.

Comparación de la espondilitis reumatoide y de la fluorosis mutilante

SUMARIO

(1) Se determinaron las cifras de fluor en fragmentos de autopsia de costillas, sacro, ilión, vértebras, tejidos blandos adyacentes y médula costal de un sujeto con espondilitis reumatoide de 10 años de duración. Las cifras de fluor no rebasaron las normales. En este caso la condensación ósea que se suele encontrar en esta enfermedad no fué debida al aumento de los depósitos de fluor en los tejidos del sistema locomotor.

(2) Se presenta una comparación tabulada de la espondilitis reumatoide, de la fluorosis mutilante y del carcinoma metastásico.

Ann. rheum. Dis. (1955), **14**, 385.

CHANGES IN THE CORIUM AND SUBCUTANEOUS TISSUES AS A CAUSE OF RHEUMATIC PAIN

BY

DORIS M. BAKER

London

(RECEIVED FOR PUBLICATION 9 MAY, 1955)

In a previous communication (Baker, 1951), an account was given of a clinical syndrome called panniculitis, and it was suggested that the morbid anatomy was different from that hitherto described. The condition is common at the menopause, whether natural or artificial, probably for two reasons:

(1) there is often a rapid increase in weight;
(2) there is a readjustment in endocrine function.

The syndrome can also occur in quite young people, though this is less usual.

The patient's added bulk may be evenly distributed, but commonly certain areas of the body are more affected than others. The areas usually involved are the region of the deltoid muscles, the back of the upper arm, the back of the neck, the pectoral muscles, the lumbar region, sacrum, and buttocks, the front of the lower leg, and at times the region of the heel to either side of the Achilles tendon (Fig. 1). For diagnosis a convenient spot to examine is in front of the external auditory meatus in the region of the parotid gland; of my series of cases, 70 per cent. showed the characteristic thickening at this site.

Symptoms.—The patient complains of a feeling of weight or heaviness in the affected parts, giving rise to undue fatigue on exertion. When the added bulk is in the lower limbs and the gluteal region, she is exhausted by walking; when the arms and neck are involved, lifting the arms—as in polishing, typing, or even brushing the hair—can cause fatigue, heaviness, and aching discomfort. In addition, the patient complains of a sore, bruised, or burning feeling when the affected parts are warmed —for example, before a fire or in bed at night. In bed this symptom is one cause of "fidgety legs", for the patient restlessly seeks out cool areas in the bed. The pain is usually felt in patches or areas of the body; and after being for a time in one spot—for example, the front of one thigh—it may spread to a similar position in the other limb, or to another area of the body. In addition to pain, there may be patches of numbness and a sensation of pins and needles, and when such paraesthesiae are bilateral they may cause difficulty in diagnosis. These patients bruise easily, and this may first lead them to seek advice.

Signs.—With this syndrome two main signs are found. First, the skin is tacked down over the affected part so that it is impossible to lift it away from the underlying tissue, and mottling or a *peau d'orange* effect is produced when the skin texture is tested by palpation. Secondly, over the affected area the skin feels dense, almost indurated, with a lack of elasticity; one of the easiest areas in which to elicit this sign is in front of the external auditory meatus. Many of the indurated areas may be tender on palpation, the tissues feeling bruised or sore. Where the patient complains of numbness, sensation is diminished. Finally, with involvement of the tissues of the face, other than the part, in front of the ear, the appearance is altered by the ironing out of the small lines and wrinkles which give character to the face, and the features may become coarsened.

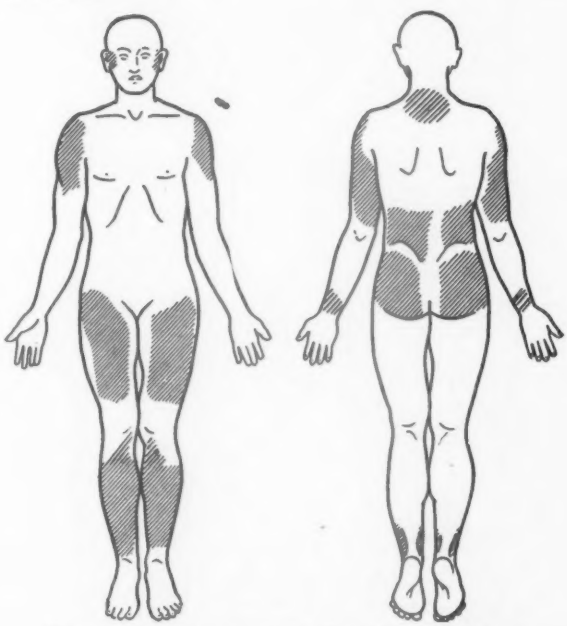


Fig. 1.—Areas most commonly affected by this syndrome.

The following is a typical case history:

Case 1.—An unmarried woman, aged 51, complained that for 7 weeks she had had burning pain in the front of the left thigh, accompanied by a feeling of numbness and pins and needles. After 2 weeks the pain spread to the front of the right thigh. The limbs felt heavy, and the symptoms were aggravated when she got warm in bed, making her restless and disturbing her sleep; she noticed that she bruised easily. Her weight had increased by over 1 stone in the past 2 years.

No evidence of organic disease was found; but the skin of the thighs showed changes typical of panniculitis and the area of skin in front of the external auditory meatus was tightly tacked down and thickened. Radiographically the hip and knee joints proved normal. Biopsies of skin from the thigh and the arm were compared; that from the thigh showed greater thickness and density of collagen in the dermis than sections from the arm and from a normal thigh.

Progress.—After 3 weeks on a strict low-sodium diet, the patient reported that at first she had been relieved but that latterly the symptoms had returned.

When she was seen 4 months later, the pain and discomfort in the thighs had not improved, except at night when she was less restless. In the lower part of both buttocks there was now a bruised and burning feeling, which seemed to radiate into the groins; it felt "as if the skin was too tight for the flesh". The skin over the lower part of the buttocks was thickened, tacked down, and very tender; and over the region of the

FIG. 2(*a*).—Case 2, showing enlarged area of thighs.

FIG. 2 (*b*).—Case 2, normal skin from inner side of thigh.

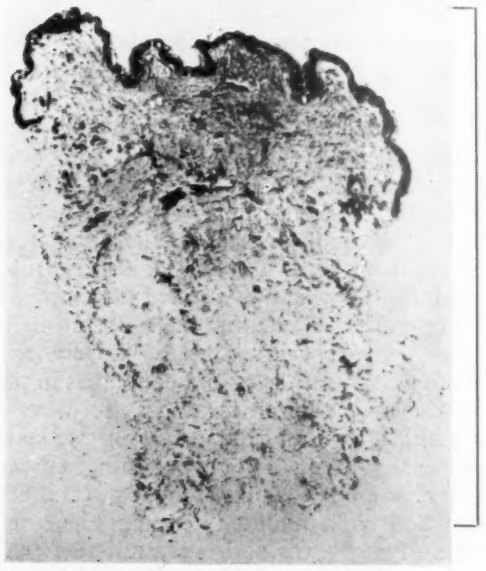


FIG. 2(*c*).—Case 2, skin from painful area.

7th cervical vertebra there was a patch of indurated skin which on palpation gave a sensation of pins and needles.

In general the presentation is as described above, but other manifestations occur of which the following two cases are examples:

Case 2.—A married woman, aged 59, who had had the menopause at the age of 58, came complaining that she was developing "painful tumours" over both hips. The swelling had appeared over the right hip first and had then developed on the left side; she could not lie on her side at night. She had put on a stone in weight over the past 2 years. The patient was organically sound, but over the lateral aspect of each hip there were large pads of indurated tender skin and subcutaneous tissue 8 in. in diameter (Fig. 2*a-c*).

Case 3.—An unmarried woman, aged 33, was sent to my general medical out-patients' clinic as she was complaining of swollen legs. Her doctor wrote:

> I cannot detect any organic disease of the heart or kidneys to account for this patient's condition, but there is marked swelling of both thighs which feel wooden on palpation and are tender to the touch, the skin seems tied down. Her stockings which normally are loose are now cutting into her thighs.

The patient, on questioning, said she had been putting on weight rapidly during the past year. Her thighs were painful to the touch, the pain was a sore, burning one and it became worse at night in bed. Clinical examination revealed no evidence of organic disease, but the skin of the thighs was tacked down to the underlying tissues, dense, and tough and tender on palpation (Fig. 3*a-c*).

FIG. 3(*a*).—Case 3, showing normal contour of limbs.

FIG. 3(*b*).—Normal skin for comparison.

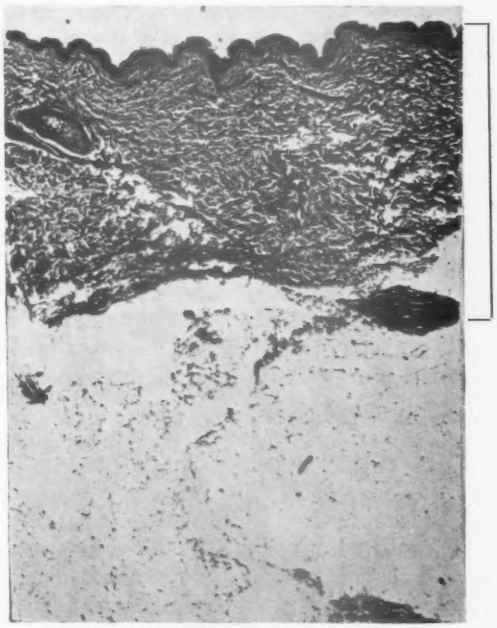


FIG. 3(*c*).—Skin from affected area.

Morbid Anatomy

Stockman (1911) and Telling (1936) described this condition as an inflammation of the panniculus adiposus with an invariable tendency to proliferative thickening, secondarily involving the nerve fibres in the form of a neuritis. Kling (1937) and Copeman (1949) reported that they found no evidence of inflammatory change. Haram (1951), after examining five skin biopsies, three from pathological areas of skin and two from normal skin, reported that the dermis appeared to be thicker in the three pathological sections than in the two normal sections, with denser collagen bundles in the reticular layer of the former. The subcutaneous fat showed no pathological change, and there was no round celled infiltration or other evidence of inflammatory change in either the epidermis, dermis or subcutaneous tissues. Since 1951, 49 skin biopsies have been taken from patients suffering from this syndrome and seven biopsies from normal skin for controls; five of the latter have been taken from apparently normal areas of skin in patients suffering from this syndrome in other parts of the body. Haram found in 80 per cent. an apparent increase in depth and in some cases in density of the collagen layer of the dermis and in some sections the collagen appears to dip down into the fatty tissue. The collagen fibres were mature and acellular. The subcutaneous fat showed no pathological change and there was no evidence of inflammatory change. Electron microscopic examination of the collagen tissue shows that the period of the striations of the collagen fibrils and the diameter of the individual fibrils is no different from those of normal skin.

Thus these changes confirm the statement that there is no evidence of inflammatory change in this condition, but they also suggest that there is an increase in the depth of the collagen layer in a high percentage of the skin biopsies examined, varying from slight to considerable. The best evidence so far comes from cases where an area of skin from the painful part of a limb is compared with a biopsy from apparently normal skin in the same limb. In the future this would appear to be the only valid comparison to make, although comparison with the skin of the opposite limb might seem suitable. (Figs 4 and 5.)

Correlation between Signs, Symptoms, and Morbid Anatomy

Before attempting a correlation between the pathological findings and the signs and symptoms, a short description is necessary of certain relevant features of normal skin. According to Lever (1949), collagen forms 98 per cent. of the connective tissue of the corium or dermis; the bundles are only slightly extensible but are wavy and so permit of stretching of the skin. The collagen bundles are interwoven with a web of elastic fibres which in the papillae run upward and split into fibrils; this contributes to the firm coherence between the epidermis and the dermis, since the elastic fibrils are rigid and will not stretch.

In the syndrome described above it would seem probable that the *peau d'orange* or mottled appearance of the skin results from the rapid increase in the fat and collagen deposited under the epidermis; this would stretch the epidermis except in those parts held in position by the so-called elastic fibrils.

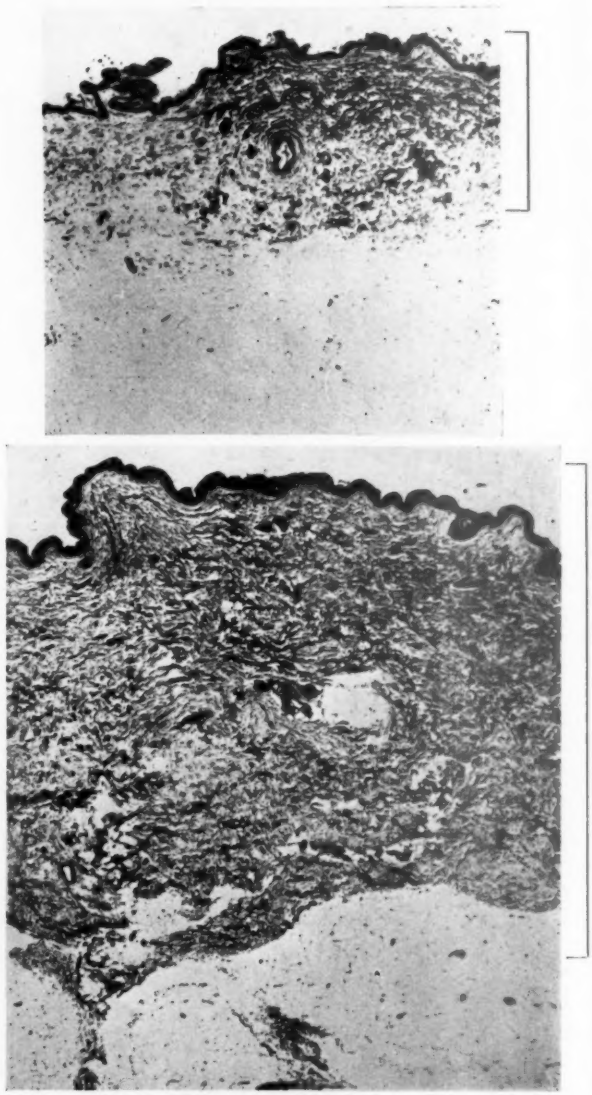


Fig. 4.—Skin from normal thigh (above), compared with skin from affected area (below).

The pain and tenderness of the tense tissues may well be due to pressure on the small nerve endings with which the dermis is freely supplied. The patient feels the burning pain characteristic to the skin and there would also be paraesthesiae and tenderness on palpation. Aggravation of the symptoms by warmth would be produced by the vasodilatation of the numerous small blood vessels in the dermis, adding to the tension in the tissues.

Although increased depth of the collagen layer of the dermis would seem to be a major factor in producing the signs and symptoms in this syndrome, there is one other major factor, rapid increase in adipose tissue, and possibly a third, water retention.

Without exception, all the patients in my series gave a history of a rapid increase in weight. This seemed to have the purely mechanical effect of increasing the tension under the epidermis. No pathological change was detected in the fatty tissue, and obesity in itself is not a source of pain. It seems possible, however, that the adipose tissue could play a part in water retention, and abnormal water retention would be an added source of tension in the affected tissues. An experiment carried out by Copeman and Pugh (1945) gives some support to the theory of water retention; they selected 22 patients believed by them to be suffering pain due to increased fluid tension. By well-planned measures they obtained obligatory diuresis, designed to reduce the volume of the body fluid by extra-cellular, intracellular, and general dehydration; thirteen of the 22 patients were freed from pain for varying periods.

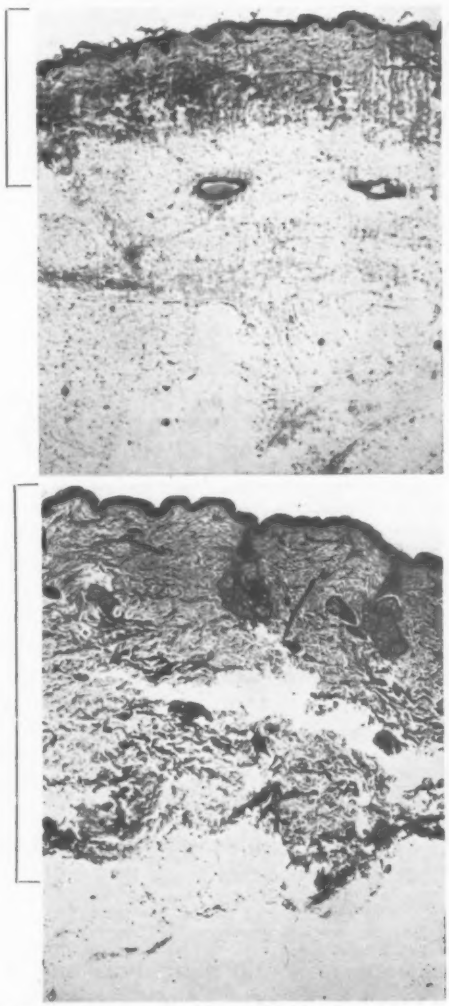


Fig. 5.—Skin from normal arm (above), compared with skin from painful shoulder (below).

Prognosis

Since patients suffering from this syndrome with symptoms of sufficient severity to make them seek help at a clinic for rheumatic diseases are few in number, any statement as to prognosis must be drawn from personal experience only. The impression is that this is a self-limiting condition and that ultimately the symptoms disappear. The speed with which this takes place varies very much and is undoubtedly influenced by treatment. It seems reasonable to suppose that the epidermis will, in time, adjust itself to the added tension in the dermis, and that this will happen more quickly if the patient loses weight. In a follow-up of fifty patients over a period of 3 years, the important point emerged that those who lost an appreciable amount of weight were relieved of their symptoms, whereas those who remained stationary or gained in weight still have their complaints. Whether the collagen content of the dermis returns to normal there is so far insufficient evidence; it is not easy to gain consent to a biopsy of skin once a patient feels she has recovered.

Incidence

Enough cases have not yet been collected to warrant a statistical survey, but calculations based on the number of proved cases seen during one year at two clinics for rheumatic diseases suggest that approximately 0·5 per cent. of all female patients are suffering from some form of this syndrome.

Treatment

Although this would appear to be a self-limiting condition, it may give rise to symptoms for a period of years. My follow-up of a series of fifty cases covers 4 years and shows that after 3 years patients can still have symptoms, although some become symptom-free in a few months. Because no one is willing to endure discomforts for an indefinite length of time, some form of treatment is essential; promise of eventual relief is not enough. The

main purpose of treatment is to reduce the tension under the epidermis, thereby relieving the pressure on the small nerve endings.

General Measures.—The first requirement is gradual but steady reduction in weight; the loss must go on until the patient is back to or a little below their usual weight before the rapid increase. This can be achieved, if the patient co-operates, with a 1,000-calorie diet or any good reducing diet. Since water retention may be a factor in this syndrome, a low-sodium intake is also required. If there are no contraindications small doses of thyroid can be prescribed.

These patients are entitled to analgesics, particularly to give them freedom from pain at night.

Physical Measures.—One of the most useful measures is planned general exercises, and the patient should be taught a simple scheme to carry out daily. Any form of heat or hydrotherapy, because it produces vasodilatation, is a painful form of treatment. Local measures such as massage to loosen up the tissues have a limited value and can be used in cases where small areas are involved.

Special Measures.—Phenylbutazone, so long as it does not induce water retention, seems to give a fair measure of relief and can be prescribed in suitable cases. Eight patients were materially relieved while taking 0·2 g. twice daily, but three had some aggravation of their symptoms and there was some indication of water retention.

Cortisone was given to a small series of patients in doses of 75 mg. daily. The numbers were insufficient to draw definite conclusions, but where there was no evidence of water retention there was definite relief from symptoms. This did not, however, seem a treatment to recommend in view of the problems associated with its prolonged use.

Hall (1936), trying the effect of two oestrogenic substances in a condition he termed indifferently menopausal arthritis or arthralgia, claimed substantial benefit in 90 per cent. His description of the clinical picture is very similar to the syndrome under discussion and many of his patients had no demonstrable lesions in the joints. Chaouat (1951) also found the administration of dienoestrol effective in relieving pains associated with the menopause.

Discussion

Since the majority of these patients are women at or near the menopause, it is more than suggestive that this condition is the result of some endocrine dysfunction or hormone imbalance (Copeman, 1949). At the menopause there is a cessation of ovarian activity and the blood and urine in about 80 per cent. of women contain excessive amounts of gonadotropic hormones, indicating hyperactivity of the pituitary gonadotropic apparatus; this activity can result in obesity. Water retention, if a factor in this syndrome, might point to an alteration in the functioning of the posterior pituitary gland, since re-absorption of water by the tubules is controlled by the hormone of its posterior lobe.

As for the morbid anatomy, no firm statement can be made (until a further series of biopsies have been carried out) as to the increase in the depth of the collagen in the dermis of these patients. The high percentage of positive findings so far does, however, make this change unlikely to be a chance discovery. That this increased density is found in other conditions is evidenced by a report of a similar change in Milroy's disease (Lever, 1949).

There appears to be a close link between this syndrome and deposits of painful tissue round or near joints; Kling (1937) called this condition "juxta-articular adiposis dolorosa", Copeman (1949) more simply described the lesions as "periarticular fat-pads". Kling carried out skin biopsies on six patients exhibiting this condition and reported:

> The epidermis appears to be normal. The dermis consists in some sections of loose collagen fibres and in others of denser collagen fibres. Increase in the tension of the tissues is evidenced by the frequently found induration.

From clinical observation and from five biopsies so far carried out, these dense tender deposits, found most commonly in the region of the knee joint, seem to show the same morbid anatomy changes as are found in this syndrome (Fig. 6). The position of these deposits would give rise to pain on movement of the joints and if not recognized could be diagnosed as osteo-arthritis. Gram (1930), writing on what he describes as "dolorous subcutaneous infiltrations", says that "the mobility of the knees is seldom impaired", and describes the tissues as "infiltrated and hard; a stiff armour-like infiltration".

It would seem that the greatest benefit that we can confer on these patients is to accord them the dignity of a diagnosis which entitles them to treatment and a fair measure of sympathy and understanding. Diagnosis should not be difficult, but it should never be made in the absence of the characteristic skin changes, and whenever possible these should be confirmed by skin biopsy. This clinical syndrome still lacks a title. It should not be known as panniculitis; possibly panniculosis might be a better term.

Summary

A new conception of the morbid anatomy of the clinical condition hitherto known as panniculitis is presented and correlated with the signs and

FIG. 6(*a*).—Enlarged area below patella on inner side of knees.

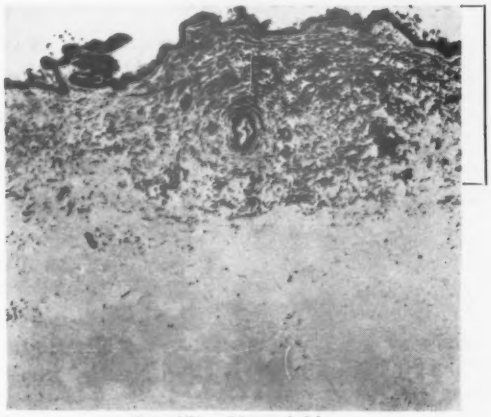


FIG. 6(*b*).—Normal skin.

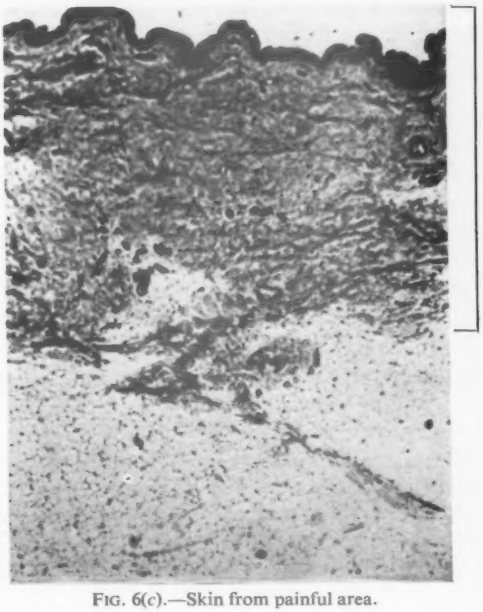


FIG. 6(*c*).—Skin from painful area.

symptoms. Some unusual aspects of the syndrome are described, and suggestions made as to aetiology. Incidence, prognosis and treatment are discussed.

My thanks are due to Dr. Joan Haram, pathologist at the Elizabeth Garrett Anderson Hospital, whose original observations led me to a further study of this syndrome; to Miss Sylvia Fitton Jackson, engaged on research into the formation and development of connective tissue, for invaluable criticism and suggestions; and to Prof. R. Hare for help and advice on the presentation of the text.

REFERENCES

Baker, D. M. (1951). *Lancet*, **2**, 753.
Chaouat, Y. (1951). *Clinique* (*Paris*), **46**, No. 436, p. 11.
Copeman, W. S. C. (1949). *Brit. med. J.*, **2**, 191.
Gram, H. C. (1930). *Acta med. scand.*, **73**, 139.
Hall, F. C. (1936). *In* "Medical Papers dedicated to Henry Asbury Christian in Honor of his Sixtieth Birthday", ed. R. T. Monroe, p. 928. Waverley Press, Baltimore, Maryland.
Kling, D. H. (1937). *Arch. Surg.*, **34**, 599.
Lever, W. F. (1949). "Histopathology of the Skin," p. 16. Lippincott, Philadelphia.
Stockman, A. (1911). *Brit. med. J.*, **1**, 352.
Telling, W. H. M. (1936). *Clin. J.*, **65**, 93.

Lésions des tissus dermiques et hypodermiques comme cause de la douleur rhumatismale

RÉSUMÉ

On présente une conception nouvelle de l'anatomie pathologique de l'affection connue en clinique sous le nom de panniculite et on la met en corrélation avec ses signes et symptômes. On décrit quelques aspects peu habituels de ce syndrome et on offre des idées concernant l'étiologie. On en discute brèvement la fréquence, le pronostic et le traitement.

Lesiones del tejido dérmico e hipodérmico como causa de dolor reumático

SUMARIO

Se presenta un concepto nuevo de la anatomia patológica de la condición clínica conocida hasta ahora bajo el nombre de paniculitis, correlacionándole con los signos y síntomas. Se describen algunos aspectos poco comunes de este síndrome y se hacen sugestiones acerca de su etiología. Se discute brevemente la incidencia, el pronóstico, y el tratamiento.

Ann. rheum. Dis. (1956), **15**, 392.

THE PRESENCE OF NATURAL HYDROCORTISONE IN SYNOVIAL FLUID

BY

C. L. COPE AND C. E. SEWELL
From the Postgraduate Medical School of London

(RECEIVED FOR PUBLICATION JULY 14, 1955)

Although the profound therapeutic effects of cortisone and similar steroids were first revealed by their action on rheumatoid joints, there is still very little knowledge of the behaviour of these steroids in joints or in tissues. It is, for example, possible that difficulties of access of blood-borne hydrocortisone to the joint cavity may be a factor in the pathogenesis of rheumatoid arthritis or other joint diseases. However, scarcely anything is yet known about the diffusion of hydrocortisone into joint spaces. We have therefore attempted to obtain some preliminary information on these matters by estimating the hydrocortisone content of samples of synovial fluid obtained from knee joints affected by rheumatoid arthritis or similar conditions.

Methods

Extraction.—To minimize possible destruction of the hydrocortisone in the joint fluid after its removal from the joint, extraction is effected as promptly as possible. The samples of synovial fluid are shaken hard with at least three volumes of ethyl acetate in a separating funnel. The supernatant solvent is poured off and the residue extracted a second, and sometimes a third time, with a further three volumes of ethyl acetate which is added to the first supernatant. If smaller volumes of solvent are used, troublesome gel formation may occur, which is not adequately resolved by centrifuging. Such trouble is reduced by using large volumes of extracting solvent. Hard and prolonged shaking is desirable to ensure optimal extraction from such a viscous fluid. The ethyl acetate is evaporated to dryness under reduced pressure at a temperature below 50° C. The residue is dissolved in acetone, one or two drops of a saturated solution of magnesium chloride in ethanol are added, and the flask is stood overnight in the cold room at 4° C. Any phospholipids present are precipitated and these are filtered off. The acetone is evaporated to dryness. The residue in the flask is dissolved in about 50 ml. petroleum ether and extracted with four portions of 50 ml. 70 per cent. aqueous methanol, which is also used to wash out any further residue from the flask. The methanol is distilled off from the separated aqueous methanol layer under reduced pressure, and the steroid is extracted from the remaining water by shaking four times with 25-ml. samples of chloroform. This chloroform is then evaporated to dryness, the residue being transferred finally to the bottom of a 10-ml. conical centrifuge tube.

Purification.—The residue is dissolved in a small volume (about 50 μl.) of a 1 : 1 chloroform-methanol mixture, and the whole is quantitatively transferred with a micro-pipette to the starting point of a paper chromatogram. Two lanes are run, one consisting of the synovial fluid extract, the other of a standard sample of 20 μg. authentic hydrocortisone (free alcohol). The papers should be of such a width that the steroid does not spread to the sides of the strip during development; a width of 4 cm. per spot is usually sufficient. The system of Burton, Zaffaroni, and Keutmann (1951) is used, in which propylene glycol is the stationary phase and toluene the mobile phase. Development is continued for 3 days. The chromatogram is then removed from the tank and dried thoroughly in a stream of warm air or with radiant heat. It is important that the propylene glycol be removed as completely as possible, and at least 12 hours drying is desirable. The dry chromatogram is then examined under ultraviolet light, whereby the reference hydrocortisone spot is revealed by its opacity and a similar opacity may sometimes be detected in the synovial fluid extract. Ultraviolet opaque spots are outlined in pencil.

Recognition of Hydrocortisone.—The dry chromatogram is now developed by dipping rapidly through the blue tetrazolium reagent (see below) and then drying in a stream of warm air. In these conditions spots where reducing steroids such as hydrocortisone are present will be revealed as bluish-violet zones where the reagent has been reduced to a coloured formazan. Excess reagent is then removed by washing the paper in running tap-water for one hour and then drying. The coloured formazan is quite insoluble in water and no loss occurs during the washing. The hydrocortisone spot is then recognized by:

(*a*) its reduction of the tetrazolium reagent;
(*b*) its opacity to ultraviolet light;
(*c*) a rate of flow on the chromatogram the same as authentic hydrocortisone.

Estimation of Hydrocortisone.—A rectangle of known area is carefully marked out in pencil to contain the hydrocortisone spot, and an equal area of paper is marked out in the region free of reducing steroid immediately below the hydrocortisone zone to serve as a reagent blank. The standard hydrocortisone spot and its appropriate blank area are similarly marked out. All four rectangles of paper are cut out with scissors, cut into small pieces, and placed in ordinary test tubes. The blue pigment is then dissolved by adding 4 ml. acid pyridine to each tube (see below) and shaking occasionally. The pigment readily dissolves, but at least one hour should be allowed for complete elution. The colour intensity of the eluate is then read in any suitable colorimeter at a wavelength of 520 mμ. The zone representing the known amount of authentic hydrocortisone, similarly eluted, serves as a standard of colour for the estimation. Under these conditions the intensity of colour is proportional to the amount of hydrocortisone present over a range from 2 to 100 μg. per spot. In trial estimations of varying amounts of hydrocortisone, a standard deviation of about 15 per cent. was obtained by this method. But with quantities of steroid below about 5 μg. per spot, the accuracy of the estimation diminishes rapidly.

When small amounts of hydrocortisone are added to large volumes of human body fluids, the amount of the added steroid recovered by this technique is about 70 per cent. of the whole (Cope, Hurlock, and Sewell, 1955). It may be presumed therefore that in such fluids the true hydrocortisone content will be about 1·4 times the amount actually found.

The efficiency of the method is dependent on an effective separation of the steroid mixture into components by the paper chromatography. With extracts from most body fluids this can usually be achieved, but with occasional extracts of synovial fluid, impurities interfere with proper development.

Two trial recoveries from synovial fluid gave the following results:

Sample A: 26 ml. gave 2·5 μg. hydrocortisone.
26 ml. + 20 μg. hydrocortisone gave 12·1 μg., a recovery of 48 per cent.

Sample B: 57 ml. gave 5·1 μg. hydrocortisone.
57 ml. + 30 μg. hydrocortisone gave 30·4 μg., a recovery of 86 per cent.

The lower recovery in Sample A was associated with a poor chromatographic separation.

Reagents

(1) *Blue Tetrazolium*

(*a*) 1 per cent. solution in methanol of blue tetrazolium;

(*b*) 1 N sodium hydroxide in 80 per cent. aqueous methanol.

Equal volumes of these two solutions are mixed immediately before use.

(2) *Acid Pyridine.* 9 vols A.R. pyridine and 1 vol. A.R. hydrochloric acid are mixed and allowed to cool.

Results

Synovial fluid samples have been divided into two groups:

(*a*) those from patients who had received no steroid therapy in any form during the preceding 4 weeks;

(*b*) those from patients who were receiving regular steroid therapy at the time of aspiration of the knee fluid.

The results for the two groups are set out in Tables I and II.

TABLE I

HYDROCORTISONE CONTENT OF SYNOVIAL FLUID IN SUBJECTS NOT RECEIVING STEROID THERAPY

Sample No.	Subject	Volume of Fluid	μg. found	μg. %	Disease
1	A	45	2·5	5·0	Rheumatoid arthritis
2	Pooled	110	4·9	4·5	Rheumatoid arthritis
3	Pooled	130	6·3	4·9	Rheumatoid arthritis
4	B	110	2·4	2·2	Reiter's syndrome
5	B	145	12·6	8·7	Reiter's syndrome
6	C	68	5·4	7·9	Rheumatoid arthritis
7	Pooled	77	5·2	6·8	Rheumatoid arthritis
8	D	81	7·5	9·3	Rheumatoid arthritis
9	Pooled	96	1·06	1·1	Rheumatoid arthritis
10	E	45	2·2	4·9	Rheumatoid arthritis
11	F	39	3·75	9·6	Rheumatoid arthritis
12	G	134	21·2	15·8	Rheumatoid arthritis
13	Pooled	96	5·9	6·1	Rheumatoid arthritis

Mean 6·8 μg. per 100 ml. ±3·61.

TABLE II

HYDROCORTISONE CONTENT OF SYNOVIAL FLUID IN RHEUMATOID ARTHRITIS SUBJECTS RECEIVING STEROID THERAPY

Sample No.	Subject	Volume of Fluid	μg. found	μg. %
14	H	50	4·0	8·0
15	H	125	12·0	10·0
16	G	82	1·6	2·0
17	Pooled	153	14·2	9·3
18	Pooled	98	9·4	9·6
19	H	43	4·1	9·5
20	F	35	4·4	12·5
21	G	60	4·8	8·0
22	E	45	4·4	9·8

Mean 8·7 μg. per 100 ml. ±2·69.

(*a*) The mean of thirteen synovial fluid samples from subjects receiving no steroid was 6·8 μg. per 100 ml. (standard deviation ±3·61).

(*b*) The mean of nine results of fluids from persons receiving steroid therapy was 8·7 μg. per 100 ml. (standard deviation ±2·69). Most of the joint fluid samples in this group were from persons receiving oral cortisone in amounts greater than 50 mg. daily, but Sample 17 consisted of pooled fluids from several joints which had received intra-articular hydrocortisone 2 weeks previously.

Although the mean for the group receiving steroid therapy is higher than the mean from persons

not given steroid, the difference between the two is little more than half one standard deviation. It is suggestive, but cannot be regarded as of real significance.

The mean and also the range of values found in the no steroid group is similar to that found in circulating blood. Our own figures for the blood hydrocortisone content, analysed by essentially the same method as has been used here for synovial fluids, are relatively few, but they range from mere traces up to 15 μg. per 100 ml. (mean 5·8 μg.).

In some instances successive joint fluid samples were taken from the same patient.

Sample 4 (Table I) was aspirated 4 days after Sample 3 from the same joint of a patient suffering from Reiter's syndrome. Both samples were analysed in an identical manner and the divergent values afford a good example of the wide range of concentration which may occur in a single joint. In this case the first sample was removed from a very tense joint and its low hydrocortisone content may have been due to an interference with free circulation through the joint by the high intra-articular pressure.

Sample 21 was from the same joint as Sample 12. In this instance the hydrocortisone content was actually lower on oral cortisone therapy.

Sample 11 was from the same joint as Sample 20. Here the use of oral cortisone was associated with a higher synovial hydrocortisone concentration.

Discussion

The results indicate that a steroid with many of the properties of hydrocortisone, and believed in fact to be that steroid, is naturally present in the synovial fluid of rheumatoid arthritic knees with large effusion. The three properties we have used to identify the hydrocortisone spot (reducing power, opacity to ultraviolet light, and proper rate of flow in the chromatogram) are not of themselves sufficient to identify the steroid appearing in the spot as true hydrocortisone. We have previously shown, however, that the spot so designated , when derived from other body fluids such as the ascitic or pleural fluid, holds a steroid having many further properties in common with hydrocortisone. Thus it has been eluted with methanol, acetylated, and then found to run on a chromatogram at the same rate as authentic hydrocortisone acetate. The eluted steroid from this spot has also been shown by us to reduce the circulating eosinophils of the adrenalectomized mouse, an effect peculiar to cortisone and hydrocortisone. We have also found that it produces a colour with the Dische reagent (Clark, 1955) which has an absorption curve identical with that given by authentic hydrocortisone and widely different from that given by many closely allied steroids. Although a non-reducing steroid having strong ultraviolet opacity may sometimes occur at this spot on the chromatogram, the evidence suggests that the only reducing steroid present in this zone is hydrocortisone. When large volumes of human ascitic fluid are extracted by the same method as used here for synovial fluid and are treated in the same manner, the amount of reducing steroid appearing at this spot corresponds with the estimated hydrocortisone content of the ascitic fluid as judged by bioassay on the adrenalectomized mouse (Cope and Hurlock, 1953). It seems justifiable to conclude therefore that the whole of the reducing steroid appearing at the hydrocortisone spot on chromatograms of synovial fluid extracts is also hydrocortisone without other reducing steroid contaminant.

The range of hydrocortisone concentrations found by us in joint fluids is the same as that found by us in random samples of blood (Cope, Hurlock, and Sewell, 1955). Our own figures for blood are relatively few, but other information on the true hydrocortisone content of blood is very scanty. There is no doubt that wide fluctuations occur. Some indirect evidence exists, however, on which an estimate of mean hydrocortisone levels may be based. Bliss, Sandberg, Nelson, and Eik-Nes (1953) have used a micro-method for estimating the plasma content of 17-hydroxy-corticosteroids, a group of steroids having in common the ability to produce a yellow colour with phenylhydrazine in sulphuric acid. Hydrocortisone gives this colour, but unfortunately one or two inert metabolites of cortisone which are present in blood give it also. Estimates based on this reaction tend therefore to be too high, but they do set an upper limit to the amount of hydrocortisone present. There are wide diurnal and other fluctuations, but these authors found a range of 3 to 26 μg. 17-hydroxy-corticosteroids (mean 13 μg.) per 100 ml. blood. Bayliss and Steinbeck (1953), using a modification of the same method, found a mean of 9·5 μg. per 100 ml. in normal blood. These workers estimated that half of the chromogenic steroid present was hydrocortisone. Their own results would therefore indicate a probable mean hydrocortisone content of 4·8 μg. per cent., whilst the figures of Bliss and his colleagues would similarly suggest an actual hydrocortisone content of about 6·5 μg. per 100 ml. blood. These estimates thus agree well with our own findings in joint fluids.

Since our own data indicate therefore that the hydrocortisone content of the synovial fluid is usually maintained at a level comparable to that found in the blood, it may be concluded that difficulty of access of hydrocortisone to the joint cavity

is an infrequent occurrence and is unlikely therefore to be a regular factor in the aetiology of the rheumatoid arthritic process.

Very little work has yet been done on the hydrocortisone content of synovial fluids although several observers have studied the fate of hydrocortisone after injection of very large amounts into the joint space. One such group was Wilson, Glyn, Scull, McEwen, and Ziff (1953), who observed in a single specimen of synovial fluid from a patient receiving oral cortisone acetate alone, a faint band having a mobility similar to that of hydrocortisone. More recently McEwen, Wilson, and Ziff (1954) have stated their experience that extracts of amounts of synovial fluid as large as 130 ml. chromatographed on very narrow papers have yielded either no bands or extremely faint ones. We believe that this pronounced difference in results between ourselves and the latter workers is probably due to minor differences of technique. We have discarded narrow strips for the paper chromatography in favour of strips sufficiently wide to prevent any steroid spreading to the edge of the paper. We find that much greater sensitivity is obtained in this way, and spots of hydrocortisone containing as little as 2 μg. can be recognized. Such sensitivity has not been possible on narrow strips which are also more difficult to handle.

Although hydrocortisone spots are regularly seen, we have never been able to detect cortisone in joint fluids even in subjects who were receiving it orally. When cortisone or cortisone acetate is ingested, some of it is rapidly converted into hydrocortisone (probably by the liver), and this soon appears in the urine. Cope and Hurlock (1954) found that, after cortisone ingestion, approximately equal amounts of hydrocortisone and of cortisone appeared in the urine. Some hydrocortisone probably enters the synovial fluid, but apparently no cortisone does so.

Evidence is accumulating from other workers that a rapid interchange of steroid occurs in rheumatoid joints. Wilson, Glyn, Scull, McEwen, and Ziff (1953) injected 50-mg. doses of cortisone and of hydrocortisone intra-articularly and found a very rapid disappearance of the steroid from the joint space. In one hour about 85 per cent. had disappeared and in 3 hours 98 per cent. The therapeutic doses injected were very greatly in excess of the naturally occurring quantities, and it is probable that much of this injected steroid was treated as a foreign body. Evidence suggesting this has been obtained by Hollander (1953) who found unchanged cortisone acetate or hydrocortisone acetate within the cells of the synovial fluid after intra-articular injection, and these observations have been extended by Zacco, Richardson, Crittenden, Hollander, and Dohan (1954). But Gallagher (1954) injected radioactive cortisone into a rheumatoid arthritis effusion and was able to show that it disappeared rapidly and at a rate similar to that of injected radiosodium. Although only scanty details are given, it seems certain that the actual amounts injected were much nearer the natural levels. It must be concluded, therefore, that a continual and fairly rapid interchange of steroid is occurring in the rheumatoid joint.

Hydrocortisone is by no means the only steroid present. Wilson, Glyn, Scull, and McEwen (1953) have noted the rapid appearance of metabolites of hydrocortisone in joint fluids after injection of the steroid. We have frequently, but not invariably, found small amounts of two reducing steroids having properties suggestive of tetra-hydro-cortisone and of tetra-hydro-hydrocortisone respectively, in joint fluids from persons who have received no steroid therapy. These steroids react with the reagent of Porter and Silber (1950); the apparent hydrocortisone content is considerably increased if this reagent is used for analysis of extracts not purified by chromatography. The amounts of these metabolites present may be greater than the amount of hydrocortisone itself. Both metabolites are physiologically inert, and it may be presumed that they also are promptly removed from the joint space as they are formed.

Summary

A substance having properties similar to hydrocortisone can be regularly detected in synovial fluid from the knees of patients with rheumatoid arthritis. Reasons are given for believing that this is true hydrocortisone.

Quantitative estimation of this substance gave a mean concentration of $6{\cdot}8 \pm 3{\cdot}6$ μg. per 100 ml. in thirteen samples.

The mean concentration in nine joint fluids from subjects receiving oral cortisone therapy was $8{\cdot}7 \pm 2{\cdot}7$ μg. per 100 ml.

The difference between the two groups is not significant.

The mean concentration in joints is similar to the mean concentration found in blood.

It is concluded that difficulty of access of natural hydrocortisone to the joint cavity is not an important aetiological factor in rheumatoid arthritis.

Our gratitude is due to many members of the Rheumatology Service of the Hammersmith Hospital for providing the samples of synovial fluid.

REFERENCES

Bayliss, R. I. S., and Steinbeck, A. W. (1953). *Biochem. J.*, **54**, 523.
Bliss, E. L., Sandberg, A. A., Nelson, D. H., and Eik-Nes, K. (1953). *J. clin. Invest.*, **32**, 818.
Burton, R. B., Zaffaroni, A., and Keutmann, E. H. (1951). *J. biol. Chem.*, **188**, 763.
Clark, I. (1955). *Nature* (*Lond.*), **175**, 123.
Cope, C. L., and Hurlock, B. (1953). *Brit. med. J.*, **2**, 753.
——, —— (1954). *Clin. Sci.*, **13**, 69.
——, ——, and Sewell, C. (1955). *Ibid.*, **14**, 25.
Gallagher, T. F. (1954). *In* "Trans. 5th Conf. Adrenal Cortex", p. 45. Josiah Macy, Jr., Foundation, New York.
Hollander, J. L. (1953). *Annals of the Rheumatic Diseases*, **12**, 347.
McEwen, C., Wilson, H., and Ziff, M. (1954). *Trans. Ass. Amer. Phys.*, **67**, 97.
Porter, C. C., and Silber, R. H. (1950). *J. biol. Chem.*, **185**, 201.
Wilson, H., Glyn, J., Scull, E., McEwen, C., and Ziff, M. (1953). *Proc. Soc. exp. Biol.* (*N.Y.*), **83**, 648.
Zacco, M., Richardson, E. M., Crittenden, J. O., Hollander, J. L., and Dohan, F. C. (1954). *J. clin. Endocr.*, **14**, 711.

Présence d'hydrocortisone naturelle dans le liquide synovial

RÉSUMÉ

On peut déceler normalement une substance ayant des propriétés d'hydrocortisone dans le liquide synovial du genou des arthritiques rhumatismaux. On donne des raisons pour croire qu'il s'agit de l'hydrocortisone même.

La détermination quantitative de cette substance dans treize échantillons donne un chiffre moyen de 6,8 ± 3,6 μg. par 100 c.c.

Le chiffre moyen pour neuf liquides synoviaux provenant des sujets recevant de la cortisone par voie buccale est de 8,7 ± 2,7 μg. par 100 c.c.

La différence entre ces deux groupes n'est pas significative.

Le taux moyen articulaire est similaire au taux moyen sanguin.

On en conclut qu'une difficulté d'accès de l'hydrocortisone à la cavité articulaire n'est pas un facteur étiologique important dans l'arthrite rhumatismale.

Presencia de hidrocortisona natural en el líquido sinovial

SUMARIO

Una substancia con propiedades de hidrocortisona se puede encontrar normalmente en el líquido sinovial de las rodillas de enfermos con artritis reumatoide. Se dan aquí razones para creer que se trata de la hidrocortisona misma.

La determinación cuantitativa de esta substancia en trece espécimenes dió la cifra media de 6,8 ± 3,6 μg. por 100 c.c.

La cifra media para nueve líquidos sinoviales de sujetos tratados con cortisona por vía oral fué de 8,7 ± 2,7 μg. por 100 c.c.

La diferencia entre estos dos grupos no es significativa.

La cifra media articular y la cifra media sanguínea son similares.

Se concluye que una dificultad de acceso de la hidrocortisona a la cavidad articular no constituye un factor etiológico importante en la artritis reumatoide.

Ann. rheum. Dis. (1955), **14**, 397.

RADIATION PAIN THRESHOLDS IN RELATION TO SKIN TEMPERATURES

BY

J. W. BEATTIE AND A. WOODMANSEY

From the Department of Clinical Medicine, University of Leeds, the General Infirmary at Leeds, and Meanwood Park Hospital, Leeds

(RECEIVED FOR PUBLICATION MARCH 21, 1955)

The marked analgesic effects experienced by rheumatic patients in this Unit after the administration of intravenous infusions of adrenocorticotropic hormone (ACTH) stimulated our interest in pain thresholds. To investigate this, it was decided to analyse the alterations in the integumentary pain threshold produced by the various drugs commonly used as analgesic, suppressive, or supportive agents for arthritic patients, since numerous articles in the literature had reported that such analgesics could be thus assessed (Slaughter and Gales, 1942; Andrews, 1942, 1943a; Chapman, Arrowood, and Beecher, 1943; Slaughter, Gales, and Johnson, 1944; Flodmark and Wramner, 1945; Leduc and Slaughter, 1945; Scott and Chen, 1946a, 1946b; Scott, Robbins, and Chen, 1946; Gross, Holland, and Schueler, 1948).

Although pain in the human integument may be produced by either mechanical, chemical, electrical, or thermal stimuli, after experimentation with various devices, a modification of the thermal radiation technique of Hardy, Wolff, and Goodell (1940), used by the investigators above, was finally adopted. This technique appeared to offer the advantages of a measurable stimulus and an end-point reasonably easily detected by the subject.

The subjective nature of pain has resulted in some misunderstanding regarding measurement. This has arisen through confusion of the perception of a "painful sensation" with the emotional and other reactions that follow the actual perceptual experience. The emotional accompaniments will depend upon the personality of the subject, but the actual perception of pain should depend only on the application of a threshold stimulus, less intense stimuli not evoking the pain sensation. This study is concerned with the pain perception threshold as represented by the verbal report of pain and not the pain reaction threshold, or the maximum tolerance of pain.

The initial experiments on certain rheumatoid arthritis patients and on the authors using corticotrophin infusions, aspirin, pethidine, and amphetamine produced discordant results. The ACTH-treated patients were experiencing feelings of warmth and flushing, while the authors felt cold after pethidine and amphetamine. Despite the extensive use of the Hardy, Wolff, and Goodell (1940) technique for analgesic testing and pain threshold estimations (*vide infra*), no critical consideration of skin temperature could be found in the literature before 1951, except the passing references of the originators. Whyte (1951), using low intensity of radiation and thus long exposures, showed that the sensations of prick-pain and of intolerable pain occurred when the skin temperature reached certain absolute values, even when different intensities of heat and different starting temperatures were used.

It was decided, therefore, to investigate the radiation pain thresholds in relation to initial skin temperatures. In a constant environment, skin temperature is conditioned by various factors, including blood flow, insensible sweating, thickness of skin, and conductivity. It did not appear necessary, therefore, to attempt to study these factors individually.

Method

A beam of light from a 500-watt lamp with compact spiral filament supplied with a rheostatically fixed current of 1·8 amp. was focused by a condensing lens through a circular aperture 1 inch in diameter, with a manually operated shutter, on to the skin of the forearm, or occasionally on to the dorsum of the hand or the forehead. The radiant energy of the instrument measured by a water calorimeter specially designed for the purpose was found to be 140 mg. calories per sq. cm. per sec. (equivalent to 8·4 pyrons). This intensity was found by trial to permit both definite recognition of the end-point and a suitable length of exposure. In all but the earliest experiments, where powdered charcoal regularly renewed

was employed, the skin was blackened with moistened carbon black and allowed to dry.

Blackening was found necessary to absorb all the radiation in order to obtain more consistent results. We preferred to use the forearm as we assumed that the patients would be less likely to give early and false signals than if the forehead were used. Hardy, Wolff, and Goodell (1952a) have confirmed that the pain threshold is roughly uniform over most of the body surface.

The duration of the stimulus was measured by stop-watch from the raising of the shutter to the patient's report that the pain threshold had been reached. The attainment of the threshold so signalled by the subject is indicated by the first sensation of pain and not the maximum amount of pain that can be tolerated. It is preceded by a sensation of heat, which increases in intensity to attain suddenly the sharp or pricking pain regarded as the "end-point".

Hardy and others (1940) used a fixed exposure to the forehead of 3 sec., the voltage applied to the lamp being altered each time until the threshold was found. Thus several applications of the beam were required to produce one threshold record. In our modification, each exposure provided one record.

In actual tests, after the subjects had become familiar with the routine, four different but adjacent areas of the skin were separately stimulated each time and the average of the four results was taken as the pain threshold value for that particular time. The skin temperature of the four sites was also measured immediately before the radiation and the results averaged. For this purpose an electric skin thermometer, based on the bridge principle, with a thermistor probe, was employed. The observations were made at not less than 15-min. intervals; preliminary skin temperature tests carried out before and 10 minutes after the pain stimulus showed a complete return to the previous level. No flare or sign of visible sweating was apparent when tests were made without blackening.

Results

The threshold for radiation pain has been defined, as by Hardy, Wolff, and Goodell, as the quantum of radiant energy necessary to evoke the sensation of prick-pain. However, for simplicity, the absolute values for the pain thresholds are not presented in the graphs. They can be found from the product of the duration of exposure and the constant of the instrument. A distinction must be made between the "apparent pain thresholds", as obtained in this manner, and the actual pain thresholds which represent the former suitably corrected for initial skin temperature.

Group 1 (Patients)

(A) In this early series, four patients (Cases 1-4) were taken at random; they were not particularly good subjects. The test areas of the forearm were dusted with charcoal. The period of the experiment included the late morning and the afternoon.

The first experience of one subject, Case 1, aged 72, is illustrated in Fig. 1. After midday when the skin temperature fell somewhat the apparent pain threshold rose; later the converse occurred.

(B) For the same four patients the effect of 15 gr. aspirin on the pain perception threshold in correlation with skin temperature was measured. The drug was given in powder form suitably disguised. In these and all subsequent experiments moistened carbon black was used.

In no case was there any marked or sustained increase in threshold level. The results in Cases 1 and 2 are shown in Fig. 2 (opposite). Here the early apparent increases in pain thresholds are accompanied by decreases in skin temperatures.

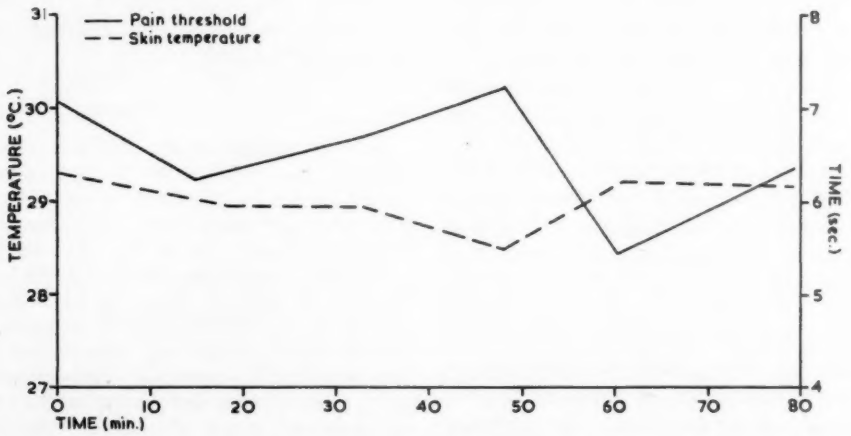


Fig. 1.—Case 1, showing variation of apparent pain threshold and skin temperature of forearm.

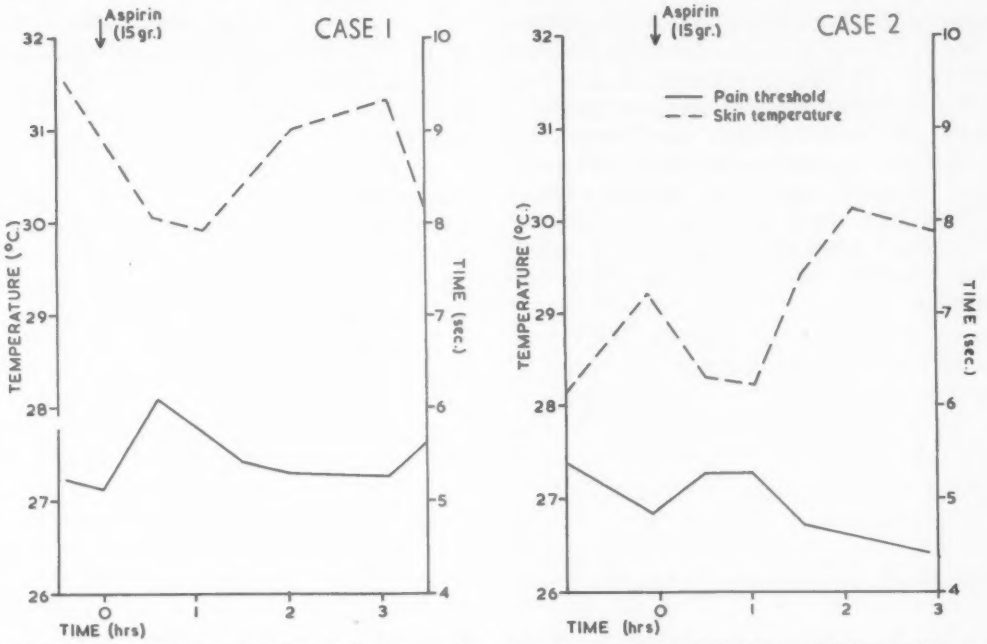


Fig. 2.—Cases 1 and 2, showing alteration of skin temperature and apparent pain threshold of forearm following 15 gr. aspirin.

(C) With the same four subjects the effect of morphine sulphate $\frac{1}{6}$ gr. by subcutaneous injection was measured.

In three patients there was an increase in the apparent pain threshold, but there was some fall in the skin temperature at the same time. The fourth subject revealed no elevation in the apparent pain threshold.

Group 2 (Observers)

(A) In these experiments the three observers (J.W.B., A.W., and B.G.L.), working in pairs, measured the pain thresholds and skin temperatures of the third member. An inverse relationship between the apparent pain threshold levels and the skin temperatures was evident.

(B) The effect of aspirin on the same three observers was measured on two different occasions in one month (October 10 and 23, 1952), using 15 gr. and 20 gr. respectively.

Fig. 3 indicates very strikingly the inverse relationship between the apparent pain threshold and the skin temperature in two of the observers.

On the second occasion two test sites (forearm and dorsum) were utilized. In one subject (B.G.L.) no gross alteration in the pain threshold occurred on either site; in another (J.W.B.) the forearm threshold remained constant while the dorsum apparent threshold rose; in the third (A.W.) the two sites showed opposite changes. There was an overall

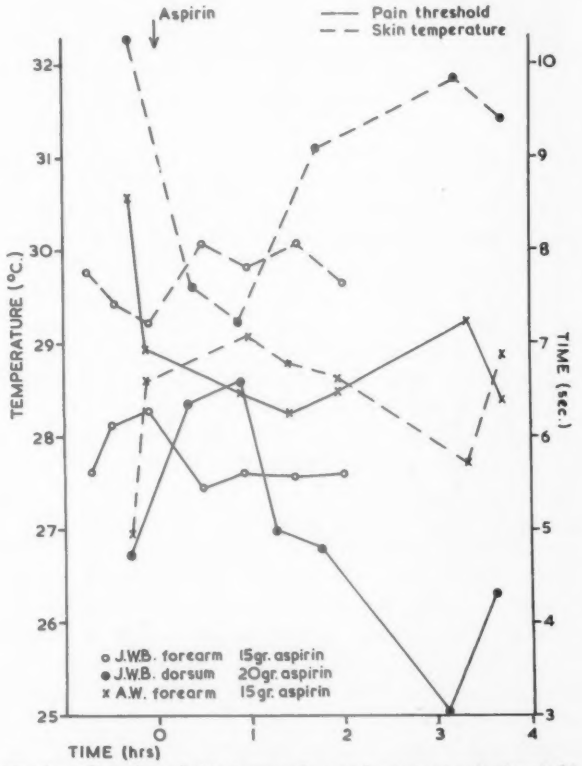


Fig. 3.—Alteration of skin temperature and apparent pain threshold in two observers (J.W.B. and A.W.) after aspirin.

inverse relationship between apparent pain thresholds and skin temperatures.

Subsequently (February 25, 1953), the two authors (J.W.B. and A.W.) were tested again after receiving 20 gr. aspirin. No change occurred in the forearm thresholds, but the dorsum apparent threshold was slightly elevated in one; nevertheless, the skin temperature correlated inversely with these alterations. This experiment indicated how difficult it would be to attribute to the aspirin any effect on the pain threshold, since the control period showed such great variations (also correlated inversely with temperature).

(C) The two authors received 10 and 20 gr. amphetamine sulphate respectively. The only change in the apparent pain threshold was a lowering in one instance, in which the skin temperature rose (J.W.B.). This experience is demonstrated in Fig. 4.

(D) The effect of antihistamines was also investigated. Phenindamine hydrogen tartrate (Thephorin, Roche) was administered on two occasions to one subject (J.W.B.) in doses of 50 mg. and 75 mg., and to another (A.W.) in doses of 75 mg. and 100 mg. Tests were carried out on the forearm and dorsum of the hand. Subsequently the effect of 300 mg. mepyramine maleate (Anthisan, May and Baker) was measured on the forehead, forearm, and dorsum of hand for each subject.

A total of fourteen tests, therefore, was carried out. The inverse relationship with skin temperature was not clearly maintained, and on many occasions there was an indication of increased pain sensitivity, especially after Anthisan.

Group 3 (Technicians).—Two technicians without previous experience and from another laboratory were given morphine sulphate $\frac{1}{6}$ gr. by subcutaneous injection. Tests were made on forearm and forehead in each case. The subjects were somewhat apprehensive, nausea and drowsiness were experienced, and there was difficulty in concentration and some apathy. There appeared to be a real increase in pain threshold, for here the inverse relationship with skin temperature was not strictly followed.

Group 4 (Authors).—In this group of experiments on the authors, the temperature of the forearm was deliberately and artificially altered. This was done by keeping one arm continually immersed first in iced water and then in hot water, to produce indirect vasodilatation and constriction in the other (test) arm. An almost perfect correlation between the apparent pain threshold level and the skin temperature was obtained (Fig. 5).

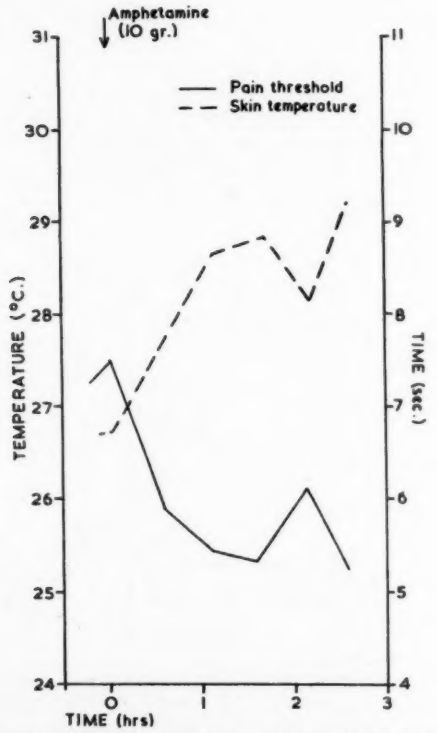


Fig. 4.—Alteration of skin temperature and apparent pain threshold of forearm after 10 gr. amphetamine. (Author J.W.B.)

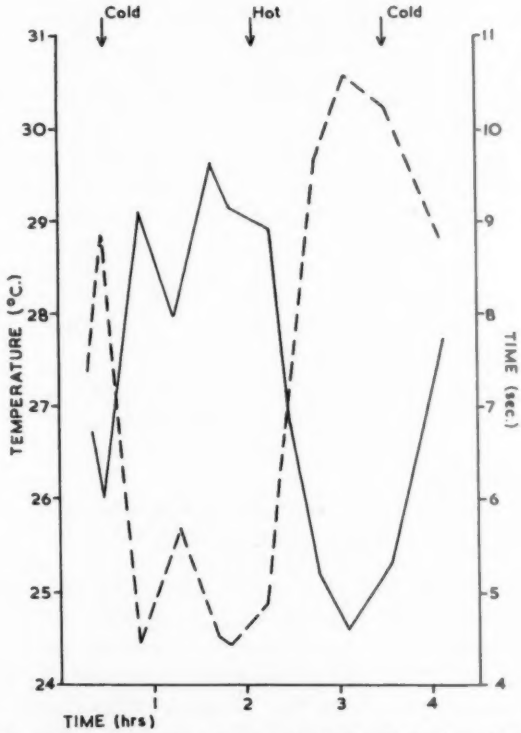


Fig. 5.—Variation of apparent pain threshold after artificial alteration of skin temperature of forearm. (Author J.W.B.)

Statistical Analysis

In the statistical examination of the results, a preliminary regression analysis for the experiments in which "artificial heating" of the tissues was used to vary skin temperatures gave an estimate of the skin temperature coefficient of $-0{\cdot}62$ sec. per °C. All pain thresholds recorded in all experiments were then compensated for varying skin temperatures, using this temperature coefficient, and the compensated thresholds were recorded on time charts and scrutinized. The time charts showed no regular pattern of variation after the administration of the drugs, and the irregularity of their patterns suggested the following method of analysis:

It was assumed that the pain threshold could be explained as a linear function of skin temperature, plus a constant depending upon the identity of the subject of the experiment, plus a constant depending upon the drug administered, plus a constant depending upon the part of the body to which the radiation was administered, plus a random term. The appropriate equation was fitted to the data using conventional multiple regression methods.

It was apparent that there were significant interpersonal differences between the different subjects. There was not, however, a significant difference between the mean thresholds of the rheumatoid arthritis patients and the rest. The results obtained at different sites on the body were not significantly different from one another. In view of the complications introduced into the analysis by the finding of significant day-to-day variations, it was decided to use a simpler and more obvious method of estimating the effects of each drug, which could not be explained from skin temperature, using the means of the compensated pain threshold values, already calculated, before and after administering the drug, the difference being taken as a measure of the effect of the drug. It was decided to combine the differences before and after administration on the different occasions on which the same drug was used in order to determine the mean effect of the drug on all occasions. Weighted means were estimated, the weighting being determined by the number of readings used before the drug was administered and also by the different quantities of the drug employed on different occasions. Estimates of the standard error of these weighted differences were prepared and these standard errors were used to provide approximate tests of the significance of the differences. Lower pain thresholds, *i.e.* smaller quanta of radiant energy, than would be expected after compensating for the corresponding initial skin temperatures were produced by aspirin, amphetamine, and Thephorin at the 5 per cent. level, and by Anthisan at the 1 per cent. level of significance. The only analgesic effects obtained followed the administration of morphia, significant at the 5 per cent. level.

Discussion

These experiments show that alterations in the apparent radiation-pain threshold of the skin are correlated with changes in the skin temperature. In most cases elevations were accompanied by decreases in the skin temperature. This effect must be taken into consideration before any apparent elevations of the threshold following the administration of various drugs are accepted.

The radiation technique of Hardy, Wolff, and Goodell (1940) has been extensively employed in the investigation of pain thresholds by many authors (including Andrews, 1943b; Chapman and Jones, 1944; Bigelow, Harrison, Goodell, and Wolff, 1945; Chapman, Finesinger, Jones, and Cobb, 1947; Schilling and Musser, 1948; 1949a, b; Hazouri and Mueller, 1950; McMurray, 1950; Clausen and King, 1950; Hemphill, Hall, and Crookes, 1952; Hall and Stride, 1954), but in no case have the authors indicated any inquiry regarding the corresponding initial skin temperatures. Thus only apparent threshold values have been obtained.

Despite the uniformity of the pain threshold as claimed by Schumacher, Goodell, Hardy, and Wolff (1940), Schamp and Schamp (1946) found a significant variability in different persons and also in the same person over a period of time, similar to that reported by Slaughter and Wright (1944). Kutscher and Chilton (1951) also found the threshold measurements "asymmetrically distributed and different among the subjects tested". Hall (1953) referred to the important effect of the variable composite factor—attitude. Our experience has also shown significant interpersonal and day-to-day differences. No variation in respect of the three separate sites utilized was observed. Furthermore, we were not able to discover any significant difference between the actual pain thresholds of the four rheumatoid arthritic patients and a normal group composed of the authors and technicians.

Many other investigators have been unsuccessful with this method in the assessment of analgesics. Ivy, Goetzel, and Burrill (1944) found a lowered pain perception threshold in about half of their subjects after 16 mg. morphine. Sonnenschein and Ivy (1949), with a similar technique, Birren, Schapiro, and Miller (1950), Kuhn and Bromiley (1951), and Whyte (1951), using aspirin, and Slaughter (1944), Chapman and Jones (1944), Dodds, Lawson, Simpson, and Williams (1945), Thorp (1946), Kuhn and Bromiley (1951), and Whyte (1951) using morphine, were also unable to substantiate the elegant parabolic curves of percentage increases in the radiation pain thresholds (actually apparent thresholds) presented by Wolff, Hardy, and Goodell (1940, 1941, 1942). Denton and Beecher (1949) found gross inconsistencies between drugs recognized clinically as effective analgesics; they observed in

some cases elevation of the pain threshold after saline and in others lowering after morphine. Kibler and Schnaper (1950) and Kutscher and Chilton (1952) observed no alteration after 1 g. procaine intravenously or the antihistamines (Pyribenzamine and Antistine) respectively.

Even Hardy and Cattell (1950) after testing 160 medical students over a period of 3 years with aspirin, codeine, and pethidine, found that their results "did not reveal any significant influence on the pain threshold measurements. Certain subjects receiving aspirin or the other agents exhibited a characteristic elevation of threshold but in others it was depressed from 10 to 20 per cent." In the face of these conflicting observations, however, they preferred to accept the results obtained without placebo controls by the three trained observers (Hardy, Wolff, and Goodell), and "concluded that untrained subjects, even of high intelligence, cannot be used successfully to measure the threshold-raising effects of aspirin, codeine, and meperidine (pethidine) in the amounts given".

We believe that the inconsistencies and discordant results reported by the above investigators with the radiation technique can be explained by the fact that no consideration was given to skin temperature. In other words, increases in pain thresholds were only alterations in the apparent pain thresholds. Our results have shown that aspirin, amphetamine sulphate, and antihistamines have no analgesic effect on the actual radiation-pain threshold. Indeed, the statistical analysis suggests a definite increase in pain sensitivity with antihistamines. Only morphine raised the actual threshold. However, in this connexion our experience is in keeping with the observations of Wolff, Hardy, and Goodell (1940), that although the subjects perceived pain they were rather indifferent to it and in addition experienced some difficulty in concentration. The morphine promoted the ability to dissociate pain perception from the anxiety reaction pattern.

Although Hardy and others (1940) realized that among the physical factors influencing the pain threshold were those tending to increase the rate of heat loss from the skin and actually stated that the skin temperature had some influence on the threshold, apparently 11 years elapsed before they considered this important factor experimentally (Hardy and others, 1951). Further, in their recent monograph, Hardy and others (1952b) have not attempted to apply their own "temperature correction factor" to their previous tests with analgesics.

Three comments are relevant. Sonnenschein and Ivy (1949) objected that the experiments of the three originators were carried out only on themselves and without placebo controls. Gregg (1951) maintained that the threshold for pain by the radiation technique was merely a critical local temperature, found by Whyte (1951), Hardy and others (1951), Cook (1952), and Wertheimer and Ward (1952) to be 46·58°, 46·1°, 44·9°, and 44·1° C. respectively. Whyte (1951) calculated from extrapolation of the data of Hardy and others that the critical local temperatures would be 46° C. for normal subjects, 50° C. after aspirin, and 54° after morphine.

We are not denying the analgesic effects of drugs such as aspirin, morphine, and antihistamines, but the experiments suggest the impossibility of correlating deep-pain analgesic efficacy with an effect on the superficial radiation pain threshold. In this respect it should be noted that Lewis (1938), and more recently Kellgren and McGowan (1948) have demonstrated the dissociation of deep-pain and skin-pain sensibility.

There appear to be the two categories of pain, that arising from exogenous superficial stimulation, not easily modified by analgesics, and that due to endogenous pathological stimulation, the alleviation of which may be brought about by modification of the underlying process.

Summary

(1) A modification of the thermal radiation method of pain stimulation with fixed intensity and variable exposure times was used in a study of integumentary pain thresholds.

(2) A distinction has been drawn between apparent and actual pain thresholds.

(3) Changes in the apparent radiation pain threshold were observed to be inversely related to alterations in the skin temperature of the area.

(4) Significant interpersonal and day-to-day differences in the actual pain thresholds were found.

(5) No definite elevation of the actual radiation pain threshold was demonstrated after administration of aspirin, amphetamine, or antihistamines.

(6) Only morphine showed an analgesic effect, although in this respect the indifference and dissociation produced may be important factors.

(7) Our experience suggests the impossibility of correlating deep-pain analgesic efficiency with effects on the actual radiation pain threshold.

(8) No significant difference was found between the range of actual skin radiation pain thresholds in the rheumatoid arthritis patients studied and in the normal group.

We are indebted to Professor S. J. Hartfall, whose patients we studied, for his constant interest and encouragement. We also thank Mr. J. D. Sargan, M.A.,

for the statistical analysis, and Miss B. G. Lawes for her technical assistance.

REFERENCES

Andrews, H. L. (1942). *J. Amer. med. Ass.*, **120**, 525.
—— (1943a). *J. clin. Invest.*, **22**, 511.
—— (1943b). *Ibid.*, **22**, 517.
Bigelow, N., Harrison, I., Goodell, H., and Wolff, H. G. (1945). *Ibid.*, **24**, 503.
Birren, J. E., Schapiro, H. B., and Miller, J. H. (1950). *J. Pharmacol.*, **100**, 67.
Chapman, W. P., Arrowood, J. G., and Beecher, H. K. (1943). *J. clin. Invest.*, **22**, 871.
——, and Jones, C. M. (1944). *Ibid.*, **23**, 81.
——, Finesinger, J. E., Jones, C. M., and Cobb, S. (1947). *Arch. Neurol. Psychiat. (Chicago)*, **57**, 321.
Clausen, J., and King, H. E. (1950). *J. Psychol.*, **30**, 299.
Cook, H. F. (1952). *J. Physiol.*, **118**, 1.
Dodds, E. C., Lawson, W., Simpson, S. A., and Williams, P. C. (1945). *Ibid.*, **104**, 47.
Denton, J. E., and Beecher, H. K. (1949). *J. Amer. med. Ass.*, **141**, 1051.
Flodmark, S., and Wramner, T. (1945). *Acta physiol. scand.*, **9**, 88.
Gregg, E. C. (1951). *J. appl. Physiol.*, **4**, 351.
Gross, E. G., Holland, H. L., and Schueler, F. W. (1948). *Ibid.*, **1**, 298.
Hall, K. R. L. (1953). *Brit. J. Psychol.*, **44**, 279.
——, and Stride, E. (1954). *Brit. J. med. Psychol.*, **27**, 48.
Hardy, J. D., and Cattell, McK. (1950). *Fed. Proc.*, **9**, 282.
——, Goodell, H., and Wolff, H. G. (1951). *Science*, **114**, 149.
——, Wolff, H. G., and Goodell, H. (1940). *J. clin. Invest.*, **19**, 649.
——, ——, —— (1952a). *Proc. Soc. exp. Biol. (N.Y.)*, **80**, 425.
——, ——, —— (1952b). "Pain Sensations and Reactions." Williams and Wilkins, Baltimore.
Hazouri, L. A., and Mueller, A. D. (1950). *Arch. Neurol. Psychiat. (Chicago)*, **64**, 607.
Hemphill, R. E., Hall, K. R. L., and Crookes, T. G. (1952). *J. ment. Sci.*, **98**, 433.
Ivy, A. C., Goetzl, F. R., and Burrill, D. Y. (1944). *War Med.*, **6**, 67.
Kellgren, J. H., and McGowan, A. J. (1948). *Clin. Sci.*, **7**, 1.
Kibler, R. F., and Schnaper, H. W. (1950). *Amer. J. med. Sci.*, **220**, 199.
Kutscher, A. H., and Chilton, N. W. (1951). *J. dent. Res.*, **30**, 822.
——, —— (1952). *Amer. J. med. Sci.*, **223**, 239.
Kuhn, R. A., and Bromiley, R. B. (1951). *J. Pharmacol.*, **101**, 47.
Leduc, E. H., and Slaughter, D. (1945). *Curr. Res. Anesth.*, **24**, 147.
Lewis, T. (1938). *Brit. med. J.*, **1**, 321.
McMurray, G. A. (1950). *Arch. Neurol. Psychiat.*, **64**, 650.
Schamp, J. R., and Schamp, H. M. (1946). *J. dent. Res.*, **25**, 101.
Schilling, R. F., and Musser, M. J. (1948). *Amer. J. med. Sci.*, **215**, 195.
——, —— (1949a). *Ibid.*, **218**, 204.
——, —— (1949b). *Ibid.*, **218**, 207.
Schumacher, G. A., Goodell, H., Hardy, J. D., and Wolff, H. G. (1940). *Science*, **92**, 110.
Scott, C. C., and Chen, K. K. (1946a). *Fed. Proc.*, **5**, 201.
——, —— (1946b). *J. Pharmacol.*, **87**, 63.
——, Robbins, E. B., and Chen, K. K. (1946). *Science*, **104**, 587.
Slaughter, D. (1944). *Anaesthesiology*, **5**, 508.
——, and Gales, J. W. (1942). *Fed. Proc.*, **1**, 167.
——, ——, and Johnson, T. U. (1944). *Quoted by* Slaughter (1944), as in manuscript.
——, and Wright, F. T. (1944). *Curr. Res. Anesth.*, **23**, 115.
Sonnenschein, R. R., and Ivy, A. C. (1949). *J. Pharmacol.*, **97**, 308.
Thorp, R. H. (1946). *Brit. J. Pharmacol.*, **1**, 113.
Wertheimer, M., and Ward, W. D. (1952). *Science*, **115**, 499.
Whyte, H. M. (1951). *Clin. Sci.*, **10**, 333.
Wolff, H. G., Hardy, J. D., and Goodell, H. (1940). *J. clin. Invest.*, **19**, 659.
——, ——, —— (1941). *Ibid.*, **20**, 63.
——, ——, —— (1942). *J. Pharmacol.*, **75**, 38.

Le seuil de la perception douloureuse de l'irradiation par rapport aux températures cutanées

RÉSUMÉ

(1) Pour étudier le seuil de la douleur cutanée on se servit d'une modification de la méthode d'irradiation thermique, consistant à la stimulation d'intensité fixe et de durée variable.

(2) On établit une distinction entre le seuil apparent et réel de la douleur.

(3) On nota que le seuil douloureux apparent variait en raison inverse de la température cutanée locale.

(4) On trouva des variations significatives du seuil douloureux réel selon le sujet et selon le jour.

(5) On ne décéla pas d'élévation nette du seuil de la perception douloureuse réelle de l'irradiation après l'administration d'aspirine, de phényl-1-amino-2-propane ou d'antihistamines.

(6) Seule la morphine révéla un effet antalgique et même ici l'indifférence et la dissociation auraient pu intervenir.

(7) Nos expériences suggèrent qu'il est impossible de déterminer un rapport entre l'effet sur la perception douloureuse profonde et l'effet sur le seuil réel de la perception douloureuse de l'irradiation.

(8) On ne trouva pas de différence significative entre les arthritiques rhumatismaux et les sujets sains étudiés en ce qui concerne le seuil réel de la perception douloureuse.

El umbral de la percepción dolorosa de la irradiación en relación a temperaturas de la piel

SUMARIO

(1) Se estudió el umbral del dolor cutáneo con una modificación del método de irradiación térmica, consistiendo en la estimulación de intensidad fija y de duración variable.

(2) Se estableció una distincción entre el umbral aparente y real del dolor.

(3) Se notó que el umbral doloroso aparente varia en proporción inversa a la temperatura cutánea local.

(4) Se encontraron variaciones significativas del umbral doloroso real según el tiempo y el sujeto.

(5) No se demostró elevación definida del umbral de la percepción dolorosa real de la irradiación después de la administración de aspirina, amfetamina (fenil-1-amino-2-propano) o de antihistamínicos.

(6) Sólo la morfina reveló un efecto analgésico, aunque aquí la indiferencia y la disociación hubieran podido intervenir.

(7) Nuestra experiencia sugiere que no es posible determinar una relación entre el efecto sobre la percepción dolorosa profunda y el efecto sobre el umbral real de la percepción dolorosa de la irradiación.

(8) No se encontró diferencia significativa entre los enfermos con artritis reumatoide y los sujetos sanos estudiados respecto al umbral real de la percepción dolorosa.

Ann. rheum. Dis. (1955), **14**, 404.

ROUTINE LABORATORY PROCEDURES IN ARTHRITIS AND RELATED DISORDERS*

BY

EDWARD F. HARTUNG AND MARY E. MAHOOD

From the Arthritis Clinic, Bellevue Hospital, Fourth Division, New York University Post-Graduate Medical School

(RECEIVED FOR PUBLICATION AUGUST 4, 1955)

The differential diagnosis of the arthritides and related disorders is mainly on clinical grounds, since there are few specific tests. The only exceptions are the infectious arthritides, where a causative organism can sometimes be demonstrated. However, a number of laboratory procedures are of confirmatory importance in diagnosis, and these may be listed as follows:

(1) Erythrocyte sedimentation rate
(2) Serum uric acid determination
(3) C-reactive protein detection
(4) Sensitized sheep-cell agglutination titre
(5) Anti-streptolysin O titre
(6) Lupus erythematosus cell test.

Superficially these appear simple to perform and interpret. The pitfalls are due to:

(*i*) the multiplicity of methods recommended, each method resulting in appreciably varying results,
(*ii*) the lack of unanimity of workers as to the best method,
(*iii*) the fact that some tests require considerable experience unless detailed instructions are laid down for the technician,
(*iv*) disagreement as to the normal values.

The diagnosis and treatment of arthritis and rheumatism are, of course, phases of internal medicine, and as our knowledge of these conditions increases it is increasingly evident that rheumatology, if it is a specialty, which we doubt, can never be divorced even for a moment from internal medicine in general. Therefore, it is important to stress that the particular laboratory procedures mentioned here are purely supplementary to the general laboratory procedures required in the diagnosis of internal medical conditions. In some hospitals and clinics, however, it may be found expedient, when the amount of work warrants it, to set up a specialized laboratory to perform tests of particular significance in arthritis and related disorders.

Since we have recently set up such a laboratory, it occurred to us that the experience gained in selecting the most practical and accurate procedures, and in standardizing the details of technique, would be of value to others who contemplate the establishment of such a laboratory.

There are many methods for each test, and we offer the following, with their normal values, as our selection of the most practical and accurate techniques.

(1) Erythrocyte Sedimentation Rate

There is not one step of any proposed technique for the performance of the sedimentation rate that is not subject to variation in the hands of clinicians, technicians, and investigators. It appeared to us, after many years of experience with the various methods, that the modified Westergren is the most accurate as well as the one most commonly used. Simple as it is, however, the pitfalls are numerous. Probably the most common source of error is indifferently cleaned glassware.

Materials:

(*a*) A chemically clean tube containing 0·5 ml. 3·8 per cent. sodium citrate.
(*b*) Westergren pipettes (thoroughly cleaned and dried) at least 300 mm. long and calibrated from 0 to 200 mm. The internal diameter should be at least 2·5 mm.
(*c*) Westergren supports to hold the tubes *exactly* vertical.

Technique.—Use a dry syringe to obtain the venous blood, and add 4·5 ml. to the 0·5 ml. of 3·8 per cent. sodium citrate. Mix thoroughly to prevent clotting. Draw a column of blood 200 mm. up into the Westergren pipette. Place the pipette into the support. Care must be taken to see that the pipette is exactly vertical. The fall of the column of red cells is read at the end of one hour. The result is reported as the number of mm. of

fall per hour. The test must be completed within 2 hours after the blood is drawn from the patient.

The pipettes are cleaned by immediate rinsing, and by soaking in detergent overnight. The next day they are rinsed twenty times in tap water and twice in distilled water, and then thoroughly dried.

Normal Values.—From zero to 15 mm. for men, and up to 20 mm. for woman (Coggeshall, 1953). While it is recognized that the number of red blood cells affects the rate, correction is not usually considered of enough clinical value to make the calculation worthwhile (Poole and Summers, 1952). Fasting and post-prandial specimens do not show significant variations (Hartung, unpublished data).

(2) Serum Uric Acid

Analysis of the serum has been shown to give the most accurate results (Bensley and others, 1947). If other specimens of blood are used, as whole blood or plasma, care must be taken to make note of the entirely different normal values. The method we prefer is a modification of that of Buchanan, Block, and Christman (1945).

Reagents:

(*a*) *Urea Cyanide Carbonate* (Christman and Ravwitch, 1932).—25 g. pure sodium cyanide and 50 g. anhydrous sodium carbonate are dissolved in 400 ml. distilled water. If heat has been applied to hasten solution, cool and add 75 g. urea. After solution is complete, make up to a volume of 500 ml. and filter. A slight precipitate will settle from this solution on standing, but the value of the solution for the determination remains unimpaired for several months.

(*b*) *Arsenophosphotungstic Acid* (Benedict, 1922).—In a litre pyrex flask dissolve 100 g. pure sodium tungstate (Baker or Merck) in 600 ml. water. Add 50 g. pure arsenic acid (As_2O_5), 25 ml. phosphoric acid 85 per cent., and 20 ml. concentrated hydrochloric acid. Boil the mixture for about 20 min., cool, and dilute to 1 litre. The reagent keeps indefinitely in a dark bottle.

(*c*) *Standard Uric Acid Solution.*—The stock solution should contain 1 mg. uric acid per 1 ml. It may be purchased at this concentration, or it may be made according to the published formula (Folin, 1933).

For the determination, 1 ml. stock solution is diluted to 100 ml. Therefore, 1 ml. dilution is equal to 0·01 mg. uric acid. The dilute standard is not stable and should be made up fresh for each determination.

(*d*) *Sulphuric Acid, Sodium Tungstate Mixture.*—One part, by volume, of 10 per cent. sodium tungstate plus eight parts, by volume, of M/12 sulphuric acid. The *p*H of the mixture should be $2 \pm 0{\cdot}1$. The mixture should be prepared fresh on the day of the determination.

(*e*) *Serum.*—1 ml. patient's serum. It should be clear and not haemolized.

Technique.—In a 50-ml. Erlenmeyer flask, mix 1 ml. patient's serum and 9 ml. sulphuric acid, sodium tungstate mixture. Let the mixture stand for 10 min. to assure complete precipitation of the protein. Filter through a No. 42 Whatman filter.

In a 50-ml. volumetric flask, put 5 ml. of the clear filtrate; to it add 2·5 ml. urea cyanide carbonate, 1 ml. arsenophosphotungstic acid, and dilute to 50 ml. with distilled water. At the same time prepare a blank of distilled water plus the reagents, and a standard containing 5 ml. the dilute standard in place of the patient's serum.

Let the colour develop for 1 hour, then read on a photo-electric colorimeter using 660 wave length. Set the machine at zero with the blank.

Calculations:

$$\frac{\text{Unknown reading}}{\text{Standard reading}} \times 0{\cdot}05 \times \frac{100}{0{\cdot}5} = \text{mg. per 100 ml.}$$

Alternative Method.—Uric acid may also be determined by the uricase method of Buchanan and others (1945), but for serum the difference is not significant (personal communication from Dr. T. F. Yü, 1955).

All the tubes are cleaned by soaking them overnight in detergent, rinsing them twenty times in tap water and twice in distilled water, and thoroughly drying them.

Normal Values.—These normal values are those below 6·0 mg. per cent. for men and below 5·5 mg. per cent. for women (Jacobson, 1938; Mull, 1943).

(3) C-Reactive Protein

C-reactive protein is a specific protein which appears in the body in response to a variety of inflammatory processes. It has been found in patients with pneumococcal pneumonia, acute rheumatic fever, staphylococcal osteomyelitis, and subacute bacterial endocarditis (Tillett and Francis, 1930). It has also been found in the serum of patients with rheumatoid arthritis (Hedlund, 1947) and a variety of other diseases, as myocardial infarction and cancer (Löfström, 1943). It is not, therefore, of much diagnostic significance, but indicates an acute inflammatory condition, and can be used as a measure of the response to therapy.

Materials (Anderson and McCarty, 1953):

(*a*) Capillary tubes with an internal diameter of from 0·5 to 1 mm. and 6 mm. long

(*b*) Clear serum (plasma from oxalated or citrated blood will not react)

(*c*) C-reactive protein antiserum (should be centrifuged before each using)

(*d*) A plasticine block.

Technique.—Draw the antiserum up into the capillary tube to about 1 to 1·5 cm. Then add an equal part of the patient's serum. This can easily be done by slanting the tube of serum and dipping the tip of the capillary tube into the serum. There must not be an air bubble between the two sera. The end of the capillary tube is sealed with plasticine and placed upright in a plasticine block. The tubes are then incubated at 37° C. for 2 hours and refrigerated at 4° C. for 24 hours. They are read immediately upon removal from the refrigerator. They are reported as 1† to 4†. A 1† is a narrow band of white precipitate at the point of interphase, while in a 4† the precipitate fills the tube. A 2† and 3† are the stages of precipitation in between.

Normal Values (Anderson and McCarty, 1953).—Normal serum contains no C-reactive protein. The presence of a precipitate shows that an active inflammatory process is present. If a series of tests are done over in a few weeks, the progress of the disorder may be studied.

(4) Sensitized Sheep-cell Agglutination

Heller Modification of Rose Test (Heller, Jacobson, and Kolodny, 1949)

As found by Rose, Ragan, Pearce, and Lipman (1948), the sera of patients with rheumatoid arthritis in the active stage contains a substance which agglutinates sheep erythrocytes sensitized with specific haemolysin to much higher titres than normal sheep cells. Heller and others (1949) found that the factor in the serum responsible for the agglutination of normal sheep cells was present in both normal and rheumatoid individuals, and that this normal agglutinin is variable and independent of the capacity of the sera of patients with rheumatoid arthritis to agglutinate sensitized cells. It can, therefore, be selectively absorbed without significantly influencing the titre against sensitized sheep cells. The titre thus obtained reflects the concentration of the factor in the serum associated with rheumatoid arthritis.

Materials:

(*a*) *Normal Sheep Cells.*—One volume of sheep cells is mixed with one volume of Alsevers solution as a preservative. The Alsevers solution is prepared as follows:

2·05 g. dextrose, 0·8 g. sodium citrate, and 40·2 g. sodium chloride are dissolved in 100 ml. distilled water. The *p*H should be from 6·1 to 6·2 and can be adjusted with 10 per cent. citric acid. It is sterilized in the autoclave at 15 lb. for 20 min.

The cells must be thoroughly washed. This is done by shaking them with normal saline, centrifuging at 2,000 r.p.m. for 10 min., removing the supernatant, and repeating the procedure three times. The supernatant of the last washing should be water clear. The packed cells are used for absorption (explained later). A 2 per cent. suspension in saline is also made from the packed cells. A part of the latter is diluted again with saline to make a 1 per cent. suspension for use in the test.

(*b*) *Determination of Basic Agglutination Titre.*—The agglutination titre of rabbit anti-sheep haemolysin, obtained commercially, is determined as follows:

The haemolysin is prepared in dilutions of 1 : 100, 1 : 200, 1 : 300, and so on up to 1 : 1,000. Eleven 10 × 75 mm. tubes are put in a rack. To the first ten tubes add 0·50 ml. saline, and to the last 0·75 ml. saline. Add 0·25 ml. of the various dilutions of haemolysin to the first ten tubes. Add 0·25 ml. of the 2 per cent. suspension of the sheep cells, previously prepared as above, to each of the eleven tubes. Incubate in a water bath at 37° C. for one hour. Refrigerate for 24 hours and read upon removal from the refrigerator. In the determination use a dilution double the last one which shows agglutination. For example, if the last tube to show agglutination is a 1 : 100 dilution, prepare the haemolysin for the determination in a 1 : 200 dilution.

(*c*) *Preparation of Sensitized Sheep Cells.*—To a 2 per cent. suspension of normal cells as prepared above, add an equal volume of haemolysin as determined in Section (*b*). The mixture of the two should be allowed to stand for one hour before using.

(*d*) *Patient's Serum.*—Clear serum is obtained from a clotted specimen of blood *and inactivated* at 56° C. for 30 min. For absorption of non-specific agglutinins, four volumes of serum are added to one volume of packed sheep cells and allowed to stand at room temperature for 40 min. with gentle shaking at intervals. The mixture is centrifuged and the clear serum is again added to a volume of packed cells and allowed to stand for another 40 min. The serum is again centrifuged, and the clear serum is ready for the test.

Technique.—Two series of two-fold dilutions of absorbed serum (prepared as above) are made in 0·5 ml. normal saline.

The first series consists of three tubes with the serum dilutions ranging from 1 : 3·5 to 1 : 14. To this series is added 0·5 ml. of 1 per cent. suspension of normal sheep cells, making a final dilution of 1 : 7 to 1 : 28.

The second series consists of ten tubes with the serum dilutions ranging from 1 : 3·5 to 1 : 1,792. To this series is added 0·5 ml. sensitized sheep cells making a final dilution of 1 : 7 to 1 : 3,584.

The tubes are shaken gently, incubated in a 37° C. water bath for 1 hour, and then refrigerated over night. Readings are made after gentle shaking, and recorded as complete agglutination, partial agglutination, or no agglutination. The test is valid only if there is no

agglutination in the tubes containing normal cells, thus indicating complete absorption of the normal sheep cell agglutinins. The result reported is the titre of the last tube showing partial agglutination.

All of the glassware is soaked overnight in detergent, rinsed twenty times in tap water and twice in distilled water, and then oven-dried.

Normal Values (Heller and others, 1949).—Cases with active peripheral rheumatoid arthritis give titres of 1 : 28 or higher with complete agglutination in the first two tubes. For this reason, this value is considered to be the lower limits of a positive reaction.

(5) Antistreptolysin-O Titre
(Todd, 1938)

The presence of a significant amount of the antibody, antistreptolysin-O, in human sera is an indication of a recent infection by a Group A streptococcus. The antistreptolysin-O titre is used as an aid in the diagnosis of rheumatic fever, in which the titre is increased, and in the differential diagnosis of diseases simulating rheumatic fever, but which rarely show an increased titre.

Materials:

(*a*) 0·1 ml. patient's serum
(*b*) 0·9 per cent. saline
(*c*) Freshly drawn rabbit blood
(*d*) 0·1 ml. standard serum (known titre)
(*e*) Streptolysin-O reagent (Difco).

Technique:

(*a*) *Preparation of Rabbit Blood.*—Use a sterile 18 or 19 gauge needle, a 10-ml. syringe, and 100 ml. 0·9 per cent. saline. Draw 10 ml. blood directly from the rabbit's heart and add it to the 100 ml. saline. Centrifuge at 2,000 to 2,500 r.p.m. for 7 min. Remove supernatant. Add another 100 ml. saline, mix, and centrifuge again for 7 min. Remove supernatant. Make a 5 per cent. suspension of the packed cells with 0·9 per cent. saline.

(*b*) *Dilution of Unknown Serum.*—Add 0·1 ml. of the patient's serum to 4·9 ml. 0·9 per cent. saline, thus making a 1 : 50 dilution. Place ten tubes, size 100 by 13 mm., in a rack. Using the 1 : 50 dilution, proceed as follows:

Tube No.	1 : 50 Serum (ml.)	Saline (ml.)	Serum Dilution
1	1·0	0·0	50
2	0·8	0·2	62½
3	0·6	0·4	83
4	0·4	0·6	125
5	0·32	0·68	156
6	0·24	0·76	208
7	0·20	0·80	250
8	0·16	0·84	312
9	0·12	0·88	416
10	0·10	0·90	500

(*c*) *Standard Serum.*—With each group of tests a serum with a known titre is run. A dilution must be made that will fall in the range of the serum dilution. As an example, if a titre of 8,900 is used, the serum must be diluted 1 : 5,000 to fit within the given ranges. Place thirteen tubes, size 100 × 13 mm., in a rack and proceed as follows:*

Tube No.	1 : 5,000 Dilution (ml.)	Saline (ml.)	Serum Dilution
1	0·80	0·2	6,240
2	0·70	0·3	7,140
3	0·65	0·35	7,700
4	0·60	0·40	8,300
5	0·55	0·45	9,100
6	0·50	0·50	10,000
7	0·45	0·55	11,100
8	0·40	0·60	12,500
9	0·35	0·65	14,300
10	0·30	0·70	16,700
11	0·25	0·75	20,000
12	0·20	0·80	25,000
13	0·0	1·0	

(*d*) *Test.*—All the above serum dilutions must be added to the tubes before the streptolysin reagent is rehydrated. The reagent is only stable for a short time. Rehydrate the reagent by adding 25 ml. distilled water as directed by the manufacturers. Add 0·5 ml. streptolysin reagent to each tube. Shake gently. Place racks in a 37° C. water bath for 15 min. Take out and add 0·5 ml. of 5 per cent. suspension of rabbit red blood cells. Shake gently. Put back into water bath for 45 min. Remove from bath and refrigerate for 24 hrs. Read immediately upon removal from refrigerator. The end-point is read as the last tube showing no haemolysis. The standard serum should read 8,300 plus or minus one tube. If it does not, the test is invalid.

Calculate:

$$\frac{\text{8,900 (or known titre)}}{\text{Standard reading}} \times \text{Reading of serum}$$

The pipettes are soaked in chromic acid cleaning solution overnight, rinsed twenty times in tap water and twice in distilled water, and oven-dried. The tubes are immediately rinsed, boiled in detergent for 5 min., rinsed twenty times in tap water and twice in distilled water, and oven-dried.

Normal Values (McEwen and Ziff, 1955).—Anything above 200 units is considered significant of an infection with haemolytic streptococcus. However, more important is a progressive rise of titre.

(6) Lupus Erythematosus Cells

A substance in the gamma globulin fraction of plasma from patients with systemic lupus erythematosus causes the "L.E." phenomenon to occur *in vitro* in the presence of normal blood. The L.E. phenomenon consists of the phagocytosis by a polymorphonuclear leucocyte of a mass of desoxyribonuclear leucocyte.

Technique.—Using a china-marking pencil, make three

* Personal communication from A. W. Beauheimer, Department of Microbiology, New York University.

circles on a slide. Put a drop of whole fresh blood in each circle.

Place the slide in a Petri dish kept moist by means of a damp piece of filter paper, and incubate for 20 min. Remove from incubator and wash off clots with normal saline. Flood slide with patient's plasma. Put cover slips over circles. Again place in moist Petri dish and re-incubate for one hour. Remove cover slips and air-dry slide. (It is important that the slides be air-dried.) Stain with MacNeal tetrachrome stain. Examine under the microscope, allowing at least 10 min. to a slide (Schultz, Baum, and Ziff, 1955).

In examining the slides look for the following:

"Haematoxylin bodies",
"Rosettes",
"L.E." cells.

"*Haematoxylin Bodies.*"—These are dark-purplish staining material varying in size and shape. The material is most often homogenous in consistency, similar to the L.E. inclusion, but more darkly stained. They have been shown to be depolymerized desoxyribonucleic acid, the same material which when phagocytized forms the L.E. cells.

"*Rosettes.*"—These are clusters of polymorphonuclear leucocytes surrounding a "haemotoxylin body". The appearance of a typical rosette with a free cloudy mass in the centre is highly suggestive but not diagnostic of lupus. Often these rings surround clumps of platelets. The latter are pseudo-rosettes and are not significant.

"*L.E.*" *Cells.*—A typical L.E. cell must be found before the preparation can be called positive. This is a neutrophilic polymorphonuclear leucocyte which has engulfed a purplish-staining homogenous mass which is so large that the nucleus is pushed to one side of the cell. The mass is chemically the same as the "haematoxylin body", but after it is engulfed by the cell it may vary in staining quality from pale blue to a dense purple. It is always homogenous in appearance and lacks any chromatin structure; this differentiates it from a "tart cell" with which it is often confused. The inclusion may vary in size from that of a single lobe of a polymorphonuclear leucocyte to the size of two leucocytes. Occasionally more than one inclusion is found in a cell (Dubois, 1953).

REFERENCES

Anderson, H. C., and McCarty, M. (1953). *Amer. J. Med.*, **8**, 445.
Beauheimer, A. W. (1955). Personal communication.
Benedict, S. R. (1922). *J. biol. Chem.*, **51**, 187.
Bensley, E. H., Mitchell, S., and Wood, P. (1947). *J. Lab. clin. Med.*, **32**, 1382.
Buchanan, O. H., Block, W. D., and Christman, A. A. (1945). *J. biol. Chem.*, **157**, 181.
Christman, A. A., and Ravwitch, S. (1932). *Ibid.*, **95**, 115.
Coggeshall, C. H. (1953). *In* "Comroe's Arthritis and Allied Conditions", ed. J. L. Hollander, 5th ed., p. 58. Lea and Febiger, Philadelphia.
Dubois, E. L. (1953). *Arch. intern. Med.*, **92**, 168.
Folin, O. (1933). *J. biol. Chem.*, **101**, 111.
Hartung, E. F. Unpublished data.
Hedlund, P. (1947). *Acta med. scand.*, Suppl. 196, p. 579.
Heller, G., Jacobson, A. S., and Kolodny, M. H. (1949). *Proc. Soc. exp. Biol.*, **72**, 316.
Jacobson, B. M. (1938). *Ann. intern. Med.*, **11**, 1277.
Löfström, G. (1943). *Acta med. scand.*, Suppl. 141.
McEwen, C., and Ziff, M. (1955). *Med. Clin. N. Amer.*, **39**, 765.
Mull, J. W. (1943). *J. Lab. clin. Med.*, **28**, 1038.
Poole, J. C. F., and Summers, G. A. C. (1952). *Brit. med. J.*, **1**, 353.
Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. (1948). *Proc. Soc. exp. Biol.*, **68**, 1.
Schultz, I., Baum, J., and Ziff, M. (1955). *Ibid.*, **88**, 300.
Tillett, W. S., and Francis, T., Jr. (1930). *J. exp. Med.*, **52**, 561.
Todd, E. W. (1938). *J. Path. Bact.*, **47**, 423.
Yü, T. F. (1955). Personal communication.

Ann. rheum. Dis. (1955), **14**, 409.

URICOLYSIS IN NORMAL AND GOUTY INDIVIDUALS

BY

EDWARD J. BIEN AND MORDECAI ZUCKER

From the Department of Pathology, Meadowbrook Hospital, Hempstead, New York

(RECEIVED FOR PUBLICATION JULY 6, 1955)

One of the many theories of gout has been that the hyperuricaemia in gout is due to a defect in uricolysis. Uricase has never been demonstrated in human tissue; thus this argument is on tenuous ground.

In the determination of the uric acid pool and turnover rate, Benedict and others (1949) consistently observed a discrepancy between turnover rate and excretion which they designated the uric acid excess. The excess could only be partly explained by sweating and loss through internal secretions such as the bile. In their experiments, the amount of N_{15} uric acid injected for the pool determination was low, and the extent of labelling of the nitrogenous products in the urine, other than uric acid, was not much greater than the natural abundance. Utilizing large doses of N_{15} uric acid in an effort to demonstrate significant enrichment of the urea and ammonia in urine, Wyngaarden and Stetten (1953) demonstrated significant uricolysis in normal man. It was determined that 18 per cent. of an intravenously administered dose of uric acid was degraded to other nitrogenous products that appeared in the urine, 6 per cent. was excreted in the faeces, and 78 per cent. was excreted as unchanged uric acid in a 2-week period. Repetition of the experiment in the same subject, with intestinal bacteriostasis accomplished with oral phthalylsulphathiazole, yielded essentially the same results. This was interpreted as an indication that degradation of urate by intestinal flora was not a major source of uricolysis.

It was important to demonstrate that uricolysis did not depend on the uric acid content of bile and the alkaline reaction of pancreatic juice. We have incubated juice with and without bile under sterile conditions (Seitz filtered) with dilute uric acid solutions. The rate of uric acid disappearance was measured by change of absorption at 292 μu. in a Beckman du Quartz spectrophotometer, and by total chromogen determinations by the method of Kern and Stransky, modified by Archibald (Forsham and others, 1948); 5 per cent. of the uric acid had been destroyed at the end of a 2-hour period, and 15 per cent. at the end of a 5-hour period. Since the *p*H of the duodenal secretions varied from 7·0 to 8·8, and would normally be much lower in man because of the acidity of the gastric contents, significant uricolysis cannot be accounted for by this route. In the above experiment, marked uricolysis occurred rapidly if there was bacterial contamination of the preparations.

Geren and others (1950) demonstrated the difference in fate of oral and intravenous urate, more than 91 per cent. being degraded after oral administration. The observations of Margules and Griffiths (1950) and Griffiths (1952) demonstrated the oxidation of uric acid at a physiological *p*H in the presence of a cytochrome-cytochrome oxidase system; Griffiths concluded that it is possible for urate to be oxidized in small quantities in organisms lacking uricase. Another uricolytic system at a physiological *p*H was reported by Tuttle and Cohen (1953); using leucoperoxidase coupled with a glucose-glucose oxidase system as a source of peroxide, and in the presence of C_{14} uric acid, these authors were able to demonstrate the degradation products of uric acid in this system as 33 per cent. allantoin and 20 per cent. urea. Urate incubated with uricase gave a 90 per cent. yield of allantoin. The nitrogen excretion as urea and ammonia in Wyngaarden's experiment could possibly be explained on the basis of peroxidase degradation. The uric acid degradation products involved in the cytochrome-cytochrome oxidase system have not yet been investigated. It is apparent, then, that although uricase is lacking, there exist in humans at least two enzymes capable of oxidase.

White blood cells contain approximately 2 per cent. verdo-peroxidase, and red blood cells have both peroxidase and cytochrome-oxidase activity. A fall in serum urate levels in blood from which the

formed elements have not been removed was observed by Yü (1953). Taking advantage of the above observations, an attempt was made to demonstrate uricolysis in whole blood plasma in the presence of both white and red cells.

Methods

50 ml. heparinized blood were obtained. A 5-ml. sample was removed and the remainder centrifuged. The plasma was removed and the buffy coat pipetted off. The buffy coat was centrifuged in a narrow tube in either the patient's own plasma or isotonic saline. After three to four separations, high concentrations of white blood cells, fairly free of red cells, were obtained. The red cell preparations were obtained by pipetting the red cells from the bottom of the tube and freeing them from white blood cells in the same manner as above. Each patient had the following samples incubated at 37° C. under 5 per cent. CO_2–95 per cent. O_2:

1. Whole blood.
2. Plasma.
3. White blood cells and the same patient's plasma.
4. Red blood cells and the same patient's plasma.

Blood counts were done of Preparations 3 and 4, and plasma samples from all tubes were taken at 1, 2, 4, and 24 hours. Uric acid determinations were done by Buchanan, Block and Christman method, as modified by Yü (1953). Repeat determinations on the same individual on three different occasions yielded the results given in Table I.

The final *p*H of the samples, after 24 hrs' incubation, was within 0·3 *p*H units of the original samples. The average normal sample, usually from a patient with an elevated leucocyte count, contained 52,200 white blood cells and 0·59M red blood cells per c.mm. in the white cell preparation; the red cell preparations contained an average of 4·0M red blood cells and 1,070 white cells per c.mm. The values for the preparations made on gouty individuals were of the same order. 3 ml. plasma were incubated with 0·5 ml. cell concentrate, but no attempt was made to incubate any specific amount of urate with any specific number of cells. All white blood cell preparations contained some red cells, and almost all red blood cell preparations contained some white cells.

The results obtained in a group of 25 normal subjects without hyperuricaemia (12 males and 13 females), are listed in Line 1, Table II. There was no sex difference (with regard to uricolysis) and the results for the normal subjects are combined. The results of eight determinations in seven patients in whom the diagnosis of gout was established are listed on Line 2 of Table II.

The rate of uricolysis is not dependent on the level of urate in the plasma of normal individuals and was demonstrated by the following experiment:

With uric acid added to the plasma of normal subjects, so as to bring it to hyperuricaemic levels, the rate of uricolysis was unchanged. The mean fall in urate level is obviously less in the patients with gout, but little could be told about any particular individual from the rate of uricolysis because individual variation was so great. In our limited series, there is certainly no correlation between the severity of the disease and the rate of uricolysis. In addition, all our uric acid determinations are total chromogen determinations; and it is not inconceivable that there might be liberation or equilibration with the plasma of other substances that would reduce arsenophosphotungstic acid. Uricolysis was very slight in 6 hrs, but almost complete in all in 20 hrs, in plasma incubated with:

(*a*) crude horse-radish peroxidase,
(*b*) peroxidase and peroxide,
(*c*) glucose-glucose oxidase and peroxidase.

Highly purified peroxidase preparations required the

TABLE I

PERCENTAGE DECREASE IN PLASMA URATE IN PATIENT WITH LYMPHATIC LEUKAEMIA
(Plasma Urate Level 7·4 mg./100 ml. Range 7·0–7·9)

Incubation	Whole Blood	Plasma	White Cells	Red Cells
Mean	11	+1	13	18
Range	9 to 13	−2 to +2	12 to 13	13 to 22

TABLE II

MEAN PERCENTAGE DECREASE IN PLASMA URATE AFTER INCUBATION

Subjects	No. of Determinations	Whole Blood	Plasma	White Cells	Red Cells
Normal	25	34·4	2·3	39·0	29·8
(Standard Deviation from the Mean)		(3·2)	(3·6)	(4·8)	(4·6)
Gouty	8	23·2	3·5	26·5	19·2
(Standard Deviation from the Mean)		(4·2)	(3·5)	(0·5)	(2·9)

presence of either peroxide or glucose and glucose oxidase before uricolysis occurred.

Summary

Uricolysis occurs in whole blood as well as in plasma incubated with white or red blood cells. It is conceivable that the diminished rate of uricolysis in gouty patients could contribute to the hyperuricaemia. The rate of uricolysis does not apparently depend on hyperuricaemia, as there is a marked difference between the rate of uricolysis found after raising normal plasma to a hyperuricaemic level by the addition of urate, and that found in the hyperuricaemia of gout.

We wish to express our thanks to Mrs. Phyllis Faber for her technical assistance.

REFERENCES

Benedict, J. D., Forsham, P. H., and Stetten, D., Jr. (1949). *J. biol. Chem.*, **181**, 183.

Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G. (1948). *J. clin. Endocr.*, **8**, 15.

Geren, W., Bendich, A., Bodansky, O., and Brown, G. B. (1950). *J. biol. Chem.*, **183**, 21.

Griffiths, M. (1952). *Ibid.*, **197**, 399.

Margules, L., and Griffiths, M. (1950). *Arch. Biochem.*, **29**, 225.

Tuttle, A. L., and Cohen, P. P. (1953). *Fed. Proc.*, **12**, no. 1, 281.

Wyngaarden, J. B., and Stetten, D., Jr. (1953). *J. biol. Chem.*, **203**, 9.

Yü, T. F. (1953). Personal communication.

Uricolyse chez sujets normaux et goutteux

RÉSUMÉ

L'uricolyse a lieu aussi bien dans le sang complet que dans le plasma incubé avec des globules blancs. Il est concevable que le taux bas d'uricolyse chez les goutteux contribuerait à, ou serait responsable de l'hyperuricémie. Le taux d'uricolyse ne depend pas apparemment de l'hyperuricémie, parce qu'il y a une différence marquée entre le taux d'uricolyse du plasma normal rendu hyperuricémique par l'addition d'urate et celui du plasma hyperuricémique goutteux.

Uricolisis en sujetos normales y gotosos

SUMARIO

Uricolisis ocurre en la sangre completa así como en el plasma incubado con globulos blancos. Se puede concebir que las cifras bajas de uricolisis en los gotosos contribuyen a, o sean responsables de la hiperuricemia. Aparentemente, la tasa de uricolisis no depende de la hiperuricemia, ya que hay una diferenica marcada entre las cifras de uricolisis del plasma normal hecho hiperuricémico con adición de urato y las del plasma hiperuricémico gotoso.

Ann. rheum. Dis. (1955), **14**, 412.

AMERICAN RHEUMATISM ASSOCIATION

PROCEEDINGS OF THE ANNUAL MEETING, 1955

The annual meeting of the American Rheumatism Association was held at Atlantic City, New Jersey, on June 3 and 4, 1955, under the presidency of Dr. Edward W. Boland of Los Angeles. Abstracts of thirty papers and the discussions thereon are printed below. One session was arranged in conjunction with the American Council on Rheumatic Fever and Congenital Heart Disease. Dr. Boland's presidential address formed part of the panel discussion on "New Analogues of Adrenocortical Steroids" (Moderator: Dr. J. J. Bunim). A second panel discussion was held on "Reconstructive Surgery in Arthritis" (Moderator: Dr. Albert J. Key).

Some Aspects of the Chemistry of the Ground Substance of Connective Tissue. By MAXWELL SCHUBERT, *New York, N.Y.* (By invitation.)

Of the three major groups of components of connective tissue, the cells, fibres, and ground substance, the last was considered in connexion with its lubricating, transport, and salt-and-water-binding properties.

The chemical structures of the mucopolysaccharides as at present understood were reviewed, and the properties of solutions of these polysaccharides considered, especially their peculiar behaviour as electrolytes. A clear understanding of the actual distribution and shapes in solution of these long, linear, highly-charged molecules is important in relation to viscosity, ion-binding, water-binding, dye-binding, and the behaviour of ground substance as a membrane. In many connective tissues the mucopolysaccharides are not free but are bound to protein, yet even in such higher complexes they retain their characteristic properties, since their ionic groups are not bound to the proteins to any measurable extent. With proteins that are sufficiently basic, either mucopolysaccharides or mucoproteins can form water-insoluble products. This is thought to be a possible basis for the formation of fibrinoid in rheumatic nodules.

Effects of Leucocytes and Rheumatoid Synovial Membrane on the Viscosity of a Mucoprotein obtained from Cartilage. By MORRIS ZIFF, H. JOEL GRIBETZ, and JOSEPH LOSPALLUTO, *New York, N.Y.*

The effects of cell-free extracts of leucocytes from peripheral blood and of rheumatoid synovial membrane on the properties of a viscous mucoprotein obtained from cartilage were described with reference to the enzymatic alteration of a cartilage constituent by extracts of rheumatoid synovial membrane and local inflammatory cells.

Extracts of human leucocytes and of synovial membrane were prepared by freezing and thawing in distilled water. The substrate was a viscous mucoprotein containing 75 per cent. chondroitin sulphate and 25 per cent. protein, isolated from cartilage. A rapid fall in the viscosity of the mucoprotein was observed, with extracts both of leucocytes and of rheumatoid synovial membrane. The fall in viscosity paralleled that obtained with crystalline trypsin. The amount of fall in viscosity was proportional to the concentration of added extract, and was not changed by adding reducing agents or a variety of proteins. The activity of the extracts showed a maximum *p*H between 5·2 and 6·5; the temperature coefficient of the reaction was 2·5. Heating the extracts rendered them inactive. Soya bean inhibitor blocked the effect of trypsin, but not that of the leucocyte or synovial membrane extracts. Extracts of mouse kidney, lung, liver, and spleen, and of synovial membrane from a patient with osteo-arthritis prepared in a similar manner showed no activity. Solutions of sodium hyaluronate were unaffected.

Sorensen titration has shown that approximately 0·5 per cent. of the nitrogen of the protein residue is split when the viscosity is reduced approximately 50 per cent. Titration of reducing sugar showed no increase in the latter. Recovery of the mucoprotein from solution by precipitation with potassium acetate and alcohol after the viscosity had been reduced demonstrated no change in the nitrogen to hexosamine ratio, but release of chondroitin sulphate from the protein was demonstrated using paper chromatographic technique.

The reduction in viscosity appeared to be due to an enzymatic reaction. The absence of profound change in the composition of the mucoprotein indicated that the fall in viscosity was due to a small but critical change in the composition of the mucoprotein molecule.

If the cartilage mucoprotein may be considered representative of ground substance mucoprotein in general, similar changes may be postulated in association with inflammation in connective tissue disease.

Discussion.—DR. JOHN H. VAUGHAN (*Richmond, Va.*): Has Dr. Gribetz studied normal and rheumatoid arthritic white cells to detect whether there might be any difference between such white cells in this enzymatic activity?

Are we to presume that the white cells themselves in the inflamed synovial membrane contribute to this activity?

DR. GRIBETZ: On a nitrogen basis we have found that the white cells in rheumatoid as well as non-rheumatoid patients showed about equal activity.

We do feel that it is the white cells, or perhaps the lymphoid molecules, which are supposed to be present in the chronic inflammatory tissue of the synovia, and that they contribute towards the activity.

We used a great many of the non-inflamed or non-rheumatoid synovia and found no activity at all.

DR. J. E. WARREN (*Pittsburgh, Pa.*): Why were the extracts from spleen inactive if the lymphocytes were the active principle?

DR. GRIBETZ: We repeated the experiment with a variety of animals—guinea-pig, rabbit, rat—and always found the spleen inactive. Some more recent work seems to indicate that there may be something inhibitory in splenic extracts, but this work is too recent to elaborate upon. We tried a variety of extraction procedures, but had no activity with splenic extracts.

Experimental Studies on Protracted Hypersensitivity of the Serum Sickness Type. By FREDERICK G. GERMUTH, JR., *Baltimore, Md.*

Histological and quantitative immunological studies were undertaken with the use of homogenous foreign proteins to determine:

(*a*) the relationship between immune response and the evolution of allergic lesions;

(*b*) the effects of antigen dosage, type of antigen, and chronicity of antigen administration on the development of allergy.

The results of these studies bear on the pathogenesis of human polyarteritis nodosa and there is experimental evidence for the role of hypersensitivity in other so-called collagen diseases and glomerulonephritis.

Histological and Clinical Evolution of Lupus Nephritis.* By ROBERT C. MUEHRCKE, ROBERT M. KARK, CONRAD L. PIRANI, VICTOR E. POLLAK, and IRVING E. STECK, *Chicago, Ill.*

The microscopic changes in kidneys of 32 patients with lupus erythematosus disseminatus (L.E.D.) was studied by serial renal biopsies. Histological data were correlated with changing clinical status, clinical laboratory data, and gross and discrete renal function tests in a continuing study of the histological evolution of the kidney involvement.

Renal lesions progressed from normal to early involvement of the glomeruli—local glomerulitis—which was characterized by "fibrinoid condensation", and local cellularity. In the course of lupus nephritis, the lesion progressed to patchy glomerulitis, general glomerulitis, and thickening of the basement membrane, to form "wire loops", and to typical subacute glomerulonephritis with epithelial crescents.

Two distinct groups of patients with nephrotic oedema were observed. One group had the nephrotic syndrome (criteria of Leiter) and microscopic findings of subacute glomerulonephritis. The second group had a pseudonephrotic syndrome with low or normal serum cholesterol and cholinesterase levels. Histological study of the renal biopsy from the second group revealed severe glomerular changes with severe capillary hyalinization and digitation of glomeruli. In these patients the disease was rapidly fatal.

Urine findings and kidney histology were correlated: white blood cells and white blood cell casts were found during the stage of local glomerulitis. Persistent proteinuria was usually found with general glomerulitis. Marked impairment of renal function was observed in the "wire-loop" and glomerulonephritic stage of lupus nephritis. A fixed urine specific gravity and, in a few cases, hypertension accompanied the chronic glomerulonephritis.

Discussion.—DR. PETER FORSHAM (*San Francisco, Calif.*): In this pseudo-type, with the low cholesterol level, have you any liver function tests that would indicate that those patients have marked liver damage and that that is why the cholesterol is low?

DR. MUEHRCKE: Various tests of liver function were done on patients with the pseudonephrotic syndrome due to lupus nephritis. The cephalin flocculation, serum bilirubin levels, prothrombin time, and bromsulphophthalein retention were normal. As observed in other patients with severe lupus erythematosus the thymol turbidity was elevated, but the serum cholinesterase level was depressed below normal.

DR. THEODORE B. BAYLES (*Boston, Mass.*): Was there evidence of amyloid in these kidney biopsies?

DR. MUEHRCKE: Sections of the kidney biopsy from patients with lupus nephritis were stained with Congo red and crystal violet. There was no histological evidence of amyloid.

DR. MORRIS ZIFF (*New York City*): Could Dr. Muehrcke elaborate a little more on the effect of cortisone therapy on the course of these lesions?

DR. MUEHRCKE: Large doses of cortisone and other steroid hormones have been reported to produce glomerular lesions of rat and rabbit kidneys. Although there is much speculation on the effect of steroids on the human kidney, no definitive work has been done.

We have studied the renal function and kidney histology of patients with rheumatoid arthritis, including some who had been on prolonged cortisone therapy and have seen no renal lesions that could be attributed to steroid or ACTH therapy.

DR. MORRIS ZIFF: With these patients receiving cortisone, was the progress of this lesion influenced?

DR. MUEHRCKE: Our studies indicate that cortisone does not seem to influence the renal lesion in lupus erythematosus. Urinary findings of proteinuria, cylindruria, and azotaemia of the acute stage may disappear on cortisone therapy as the clinical course of the patient improves. These findings are probably associated with fever and dehydration rather than with lupus nephritis.

Musculoskeletal Manifestations of Disseminated Lupus Erythematosus, Polyarteritis Nodosa, Dermatomyositis, and Diffuse Scleroderma. By W. M. MIKKELSEN, H. A. ZEVELY, N. H. CHATELIN, and I. F. DUFF, *Ann Arbor, Mich.*

From the University of Michigan Hospital necropsy series fifty cases of "connective tissue disease" were reviewed. Musculoskeletal manifestations were prominent in eighteen of 21 cases of disseminated lupus erythematosus, fourteen of eighteen cases of polyarteritis nodosa, and all of five cases of dermatomyositis and six cases of diffuse scleroderma. At some time during the illness the diagnosis of rheumatoid arthritis or rheumatic fever was erroneously applied in eleven cases of disseminated lupus erythematosus, four cases of polyarteritis nodosa, three cases of dermatomyositis, and four cases of scleroderma.

Careful review of the clinical and pathological features

* This paper is given in full on p. 371 of this issue (*Annals* (1955), 14, 371).

of these cases revealed characteristic differences on the basis of which accurate clinical diagnosis was usually possible. Objective joint findings were not of differential value, but joint contracture without intra-articular disease occurred only in dermatomyositis and scleroderma. Disseminated lupus erythematosus differed from rheumatoid arthritis in the more frequent occurrence of erythematous facial eruptions, leucopenia, and renal, cardiac, and serous membrane involvement. Peripheral neuritis and gastro-intestinal symptoms were of greatest value in recognizing polyarteritis nodosa; other valuable findings included bronchial asthma with eosinophilia exceeding 25 per cent., hypersensitive renal disease, persistent unexplained fever or leucocytosis, nodular or necrotic skin lesions, intermittent testicular pain, and *x*-ray picture of "diffuse granular disease" of lung. The muscular involvement in dermatomyositis and the skin changes in scleroderma were readily distinguished from similar but milder findings in the other diseases.

The possibility of one of these diseases, and especially of disseminated lupus erythematosus, should be considered in cases of rheumatoid arthritis that are "atypical' or associated with multiple system involvement.

Discussion.—Dr. Gerald P. Rodnan (*Bethesda, Md.*): Our experience and that of others would appear to differ from that of the speaker regarding joint involvement in scleroderma. We have had the opportunity to obtain synovial biopsies from the supra-patellar bursa of a number of patients with diffuse scleroderma. Four of these had symptoms and signs of frank arthritic involvement of the hands, knees, and other joints.

In patients with symptoms and signs of arthritis, the biopsy revealed acute or chronic synovitis, with focal areas of fibrosis besides other pathological changes.

Lupus Erythematosus Cell Reaction: Its Morphology and Specificity. By M. A. Ogryzlo, *Toronto, Ont.*

The L.E. cell reaction, as commonly performed, is an *in vitro* phenomenon which may be observed in patients with acute disseminated lupus erythematosus, when plasma, serum, or serous effusions are permitted to stand for a period of time in contact with a mixture of freshly-drawn white-cell elements of the blood or bone marrow. This test has been performed on more than 880 occasions in a large variety of patients to study the morphology of the typical L.E. cell and so-called rosette, and determine the specificity of the reaction for lupus erythematosus. Coloured photographs showed clearly the sequence of events in the development of the L.E. cell and rosette, the source of the inclusion material, and the various forms which may be encountered. While the characteristic L.E. cell is a mature neutrophil, evidence has been obtained that virtually all leucocytes are capable of taking part in both the degenerative and phagocytic phases of the reaction. These include eosinophils, basophils, monocytes, lymphocytes, and even plasma cells. Although the test was positive in 28 patients with acute disseminated lupus erythematosus, it was negative in three such patients, and occasional positive reactions were observed in patients with other diseases, including nine with classical rheumatoid arthritis, and one each with scleroderma, polyarteritis nodosa, dermatomyositis, Hodgkin's disease, and haemolytic anaemia. Two patients showed a positive test during a reaction to phenylbutazone therapy and one patient after a reaction to hydralazine therapy. These observations suggest that the phenomenon may represent a particular hypersensitive state, but that it cannot be regarded as entirely specific for lupus erythematosus and may be reversible when the sensitizing agent is withdrawn.

Discussion.—Dr. C. L. Steinberg (*Rochester, N.Y.*): In the rheumatoid arthritis patients with positive L.E. cells in marrow, were many L.E. cells found in these smears, or on many occasions? My own experience is that when L.E. cells are found in rheumatoid arthritis they are much fewer in number and much more difficult to find on subsequent occasions.

Dr. Ogryzlo: All the rheumatoid arthritis patients referred to in this paper who had positive tests showed L.E. cells in from 2 to 15 per cent. of the nucleated cell count, which would have to be regarded as fairly large numbers. The proportion was relatively constant in each patient on repeated tests.

Dr. Lawrence E. Shulman (*Baltimore, N.Y.*): We also have had several cases of false positive reactions, for example, in scleroderma which at times is associated with lupus. Patients with lupus sometimes present with a picture of Hodgkin's disease, but subsequently show widespread evidence of lupus; occasionally acute haemolytic anaemia is the initial manifestation and widespread lupus is found if the patient is followed long enough.

I do not mean to say there are no false positive reactions, but that we should be cautious in these cases.

Dr. Ogryzlo: I agree with Dr. Shulman that many patients with lupus erythematosus may initially present with symptoms resembling other diseases. However, some of the patients referred to in the paper with positive tests were examined at *post mortem* and lacked the findings associated with lupus erythematosus, including the patient with Hodgkin's disease and some of those with severe, long-standing rheumatoid arthritis. In the two patients who suffered a reaction to butazolidin, the test has become negative with recovery. On a clinical basis it would be difficult to accept these patients as suffering from lupus erythematosus. I might add that I do not regard these as false positive tests, but rather as positive tests due to the presence of other diseases. There is some indication that it represents a type of immune response which is not necessarily specific for lupus erythematosus, although most characteristic for that disease. In some instances the reaction may be reversible and disappear.

Dr. John H. Vaughan (*Richmond, Va.*): I should like to ask about the lymphocyte which has apparently engulfed some nuclear material. I believe it is the experience of most people that the lymphocyte, at least under ordinary conditions, is not a phagocytic cell. Therefore, I should like to ask whether you are sure it was a lymphocyte; and how often you have seen this? If they were, indeed, lymphocytes, it represents an extraordinary stimulus to phagocytosis.

Dr. Ogryzlo: We have seen a wide variety of phagocytic cells ingesting the nuclear bodies. There is no doubt about lymphocytes being phagocytic. I could show many examples of lymphocytes and also eosinophils behaving in a phagocytic manner and taking up the altered nuclear material. They have been observed both in fixed smears and in the living motile state.

A Study of Disseminated Lupus Erythematosus diagnosed in Patients formerly considered to have Rheumatoid Arthritis. By FRANCIS W. MCCOY, MARJORIE PATTERSON, and R. H. FREYBERG, *New York, N.Y.*

As knowledge about lupus erythematosus has increased and diagnostic aids have been improved, many patients considered to have rheumatoid arthritis with complications or an atypical form of this disease were studied to determine whether they had disseminated lupus erythematosus. Typical L.E. cells were found in the blood of approximately 25 per cent. of eighty patients in this group. These patients whose diagnosis of disseminated lupus erythematosus was *based upon the L.E. cell test* were carefully re-evaluated in regard to the behaviour of the rheumatic disease and the clinical and laboratory characteristics of the non-rheumatic illnesses.

The question whether the disease currently considered to be rheumatoid arthritis is changed into a different illness by means of therapeutic agents, was discussed.

If all patients who have L.E. cells in their blood have lupus erythematosus, the following should be emphasized:

(1) Disseminated lupus erythematosus is much more common than previously considered.
(2) Disseminated lupus erythematosus usually is more often a chronic illness; in only a small per cent. of patients is it acute, severe, and fatal.
(3) The rheumatic component of disseminated lupus erythematosus may be indistinguishable from rheumatoid arthritis.
(4) Treatment for each illness is similar in many aspects.
(5) Prognosis of disseminated lupus erythematosus is better than it was formerly considered to be.

Discussion.—DR. W. K. ISHMAEL (*Oklahoma City, Okla.*): We searched for lupus cells in the blood of 1,600 consecutive admissions to our arthritis clinics, using the 2-hour clot method; 520 were diagnosed as having rheumatoid arthritis, and in sixteen (3 per cent.) of them, positive identification of the L.E. cell was made; 129 of the rheumatoid group were classed as atypical rheumatoid arthritis, and of these only one exhibited L.E. cells.

182 of the 520 rheumatoid patients were receiving cortisone at the time of admission to the clinic; thirteen of these cortisone-treated patients produced L.E. cells, as against three who had received no cortisone.

DR. CHARLES H. SLOCUMB (*Rochester, Minn.*): We carried on a similar series of studies and came to much the same conclusions as Dr. McCoy, but I feel that in rheumatoid arthritis and lupus erythematosus the prognosis is different, and that there are sufficient differences in treatment to require the clinician to be extremely careful to differentiate between the two diseases.

In a group of 67 patients with acute lupus, 93 per cent. had positive L.E. tests. In a group of 105 rheumatoids who had not had steroids, 5 per cent. had a positive L.E. test. In a group of 27 patients in whom the rheumatism was not diagnostic, 78 per cent. had lupus and were probably lupus cases.

Granted that some patients cannot be distinguished over a period of weeks or even months by their rheumatism alone and that we have to go by their systemic reaction it remains to be seen whether the 5 per cent. of patients with the positive lupus reactions are going to react differently from the other rheumatoids, and whether they will turn out to be rheumatoids or lupus patients.

Statistically, there is no set test which will distinguish between the two diseases; in favour of rheumatoid arthritis is the persistence of synovitis, joint destruction, leucocytosis, and lowered globulin, but any of those can be duplicated in lupus erythematosus.

In favour of lupus is a recurrence of the synovitis with clearing, high fever, cerebral manifestations, leucopenia and lymphocytosis, thrombocytopenia, false flocculations, and, of course, the positive L.E. test.

One other difference in our analysis is that rheumatoid patients who had been given large doses of cortisone showed a significant difference in the occurrence of positive L.E. reactions (to be reported in a later paper by Dr. Palmer). In those who had had small amounts of cortisone, the percentage remained the same: 5 per cent. had a positive L.E. cell reaction.

DR. J. ALBERT KEY (*St. Louis, Mo.*): Has any attempt been made to correlate the past history of gold therapy with these degenerative phenomena in the leucocytes? The three cases illustrated had all had gold; perhaps this rather than the cortisone, might have been a factor.

DR. MCCOY: It is very difficult to attempt to classify these patients, but we have several who exhibit a positive L.E. phenomenon, who are taking nothing but aspirin, and are relatively asymptomatic, and one of these also received one short series of meticorten.

Many patients come to our clinic from elsewhere, and it is very difficult to obtain all the facts from them.

DR. WALLACE GRAHAM (*Toronto, Ont.*): How many of the 520 rheumatoid patients had had gold therapy?

DR. W. K. ISHMAEL (*Oklahoma City*): Less than 150.

DR. CHARLES RAGAN (*New York, N.Y.*): Can Dr. McCoy tell me the number that had a positive test at 2 hours and the number that had a positive test at 24 hours? I think a positive test in 24 hours is unusual.

DR. MCCOY: Most of the patients were positive at the end of a 2-hour period. We reviewed the 24-hour and 12-hour smears incubated at room temperature to see whether the time element increased positivity.

DR. ANDRIES I. ROODENBERG (*Rochester, N.Y.*): Are there any *post-mortem* studies on patients with atypical or typical rheumatoid arthritis with positive L.E. cells?

DR. MCCOY: The only patient in the series in which we are interested who died did not die at our hospital, but at another hospital in New York City, where the pathology report sent to us was compatible with a diagnosis of disseminated lupus erythematosus. That is the only *post-mortem* study I know of.

DR. M. A. OGRYZLO (*Toronto, Ont.*): Regarding the question of gold, we have not observed any positive tests even in those with severe reactions and renal damage. At the present time we are following three such patients, one of whom showed a doubtful test but was recorded as negative because the cells were entirely typical. I feel that gold, like other sensitizing agents, may be capable of inducing a positive test, but we have not encountered one.

DR. JOSEPH J. BUNIM (*Bethesda, Md.*): A very practical and important question is whether or not the presence of an L.E. phenomenon in a patient who is considered to have rheumatoid arthritis contra-indicates the administration of gold. Such a question does not pertain to cortisone, because if we assume the patient has lupus erythematosus, cortisone is certainly indicated; but we should be clear whether gold will precipitate or intensify the systemic manifestations.

DR. MCCOY: I can only say that some of our patients who have a positive L.E. cell phenomenon have been receiving gold and are taking it now. We hope by reviewing them to find out whether they were more sensitive as a group, but the statistics are not yet available.

DR. W. K. ISHMAEL (*Oklahoma City, Okla.*): All our patients who appear to have rheumatoid arthritis with a positive L.E. cell reaction are still alive, but 50 per cent. of those with the classical stigmata of disseminated lupus erythematosus have died during the observation period of 2 years. The latter are not included in our figures as they were seen at another hospital.

Recognition and Treatment of Patients with Chronic Hypercortisonism. By HOWARD F. POLLEY, CHARLES H. SLOCUMB, L. EMMERSON WARD, and PHILIP S. HENCH, *Rochester, Minn.*

Patients who develop chronic hypercortisonism during the treatment of rheumatoid arthritis produce a syndrome of alternating periods of mental stimulation, restlessness, and lack of interest in responsibilities, alternating with periods of emotional instability, fatigability, weakness, and aching in the muscles and joints.

A pan-mesenchymal reaction occurs in many of these patients during periods of withdrawal of the hormone. The reaction may simulate flares of L.E., periarteritis, or rheumatoid arthritis. The diagnosis, treatment, and prognosis of a large group of these patients is reviewed.

Discussion.—DR. PETER FORSHAM (*San Francisco, Calif.*): This very excellent and provocative presentation calls for a few comments, for it leads one to question the rationale of maintenance corticoid therapy.

We were shown that if one has a patient on very high doses of corticoids and is then suddenly forced to reduce this dosage because of side-effects, one finds oneself in a dilemma, because the disease flares up and sometimes in a more malignant fashion than before.

We are told that this can be prevented simply by staying below the tolerable dosage. Actual daily dosages coincide closely with the estimate of the daily output of hydrocortisone by the normal human adrenal not subjected to stress, which happens to lie between 30 and 40 mg. hydrocortisone per day. If, then, we follow the safe procedure of staying below the toxic levels—toxic to some patients and not to others—we merely suppress pituitary ACTH production by amounts of hydrocortisone equivalent to the normal adrenal cortical output. What have we done by replacing the output of the adrenal cortex in man by 40 mg. of a known steroid? Why should the patient get better?

Two possibilities arise. Do we suppress some hormone from the adrenal cortex which is bad as far as the disease is concerned, and replace that by something which is essentially good for rheumatoid arthritis? Evidence for this is not readily available, but one has to keep this possibility in mind. Alternatively, although you merely suppress and replace, perhaps the exogenous hormone administered every 6 hours is more constant than the variable levels built up by the normal human adrenal cortex. This afternoon Dr. Vincent Di Raimondo is to report on the activity of the human adrenal cortex in normal subjects; it is very active in the early morning hours, very inactive in the late afternoon, and practically asleep around midnight. This may be related to the fact that the arthritic patient feels comparatively well during the day and stiffens up in the late afternoon and evening.

The maximum adrenal cortical secretion during a 24-hour period is ten times greater than the lowest point, and if you substitute for this variable level a dose of the same hormone round the clock in equal amounts every 6 hours you may be doing better for the patient.

Although the maintenance doses of hydrocortisone and related corticoids appear very small and may be expected, on logical grounds, to do little more than normal adrenals, they may possibly prove helpful by providing the type of steroid which prevents inflammatory reaction while suppressing the endogenous steroids which increase it, and by assuring a constant level in the blood, in contrast to the tidal action of the human adrenal cortices.

DR. POLLEY: Dr. Forsham has commented on a number of aspects of the problem of exogenous hypercortisonism which could not be included in the time for our presentation. He has answered his own remarks concerning the value of cortisone therapy. Our discussion is directed toward the effects of chronic *overdosage* and cannot be interpreted as indicative of the value of hormonal therapy with optimal dosage. Hormonal therapy is no more indicated for all patients with rheumatoid arthritis than insulin for all patients with diabetes mellitus or surgery for all patients with duodenal ulcer. In the factor of dosage, cortisone and related hormones may be compared to many other therapeutic substances. Complications of overdosage from digitalis, aspirin, insulin, or sedatives, for example, do not negate the value of these drugs when used in appropriate amounts. Similarly, the problems of overdosage with cortisone, corticotropin, or related hormones should not negate the therapeutic value of optimal doses of these hormones.

DR. WALTER BAUER (*Boston, Mass.*): I find it difficult to believe that all the symptoms that Dr. Polley has ascribed to chronic hypercortisonism in his patients with rheumatoid arthritis are really manifestations of hypercortisonism. He has not convinced me that the hypercortisonism causes increased inflammatory changes of the affected mesenchymal tissue. Furthermore, some of the cases that he has reported may have lupus erythematosus disseminatus and not rheumatoid arthritis. If the many changes in the mesenchymal tissue that he ascribes to hypercortisonism do occur, why are they not seen in patients with long-standing Cushing's disease?

DR. J. ALBERT KEY (*St. Louis, Mo.*): Since they have lowered their maintenance dose, what do they do about the beginning of the treatment, and how much do they give before running into danger?

Secondly, has ACTH a place in the treatment of hypercortisonism? It would seem logical to give smaller doses of ACTH to try to stimulate the adrenal cortex as you decrease your substitution hormone.

DR. POLLEY: I will respond first to Dr. Bauer's comments. We, too, have recognized that certain of the significant features of chronic hormonal overdosage in patients with rheumatoid arthritis have not been recognized in patients with endogenously-induced Cushing's syndrome. A satisfactory explanation for this difference undoubtedly awaits further study of both diseases, but it appears that the mesenchymal responses to chronic hormonal overdosage in the patient with rheumatoid arthritis differ from the reactions due to exogenous or endogenous hormonal excesses in a patient without rheumatoid arthritis.

The question whether the rheumatoid patient in whom a diffuse mesenchymal reaction simulating lupus erythematosus develops from chronic hormonal overdosage is

in reality a patient with lupus erythematosus is, of course, an important one. In our experience the rheumatoid patient with a mesenchymal reaction resulting from hormonal overdosage has generally reverted to the previous rheumatoid pattern of tissue response if the excess of hormonal dosage is satisfactorily corrected while the mesenchymal reaction is still in a reversible stage. In our studies the incidence of mesenchymal reactions among rheumatoid patients with hypercortisonism was significantly greater than among a comparable group of rheumatoid patients who had not had hormonal therapy.

In answer to Dr. Key's question, we estimate an initial hormonal dose for rheumatoid arthritis by considering first the patient's sex and age. We prefer to keep initial doses within the anticipated limits of tolerance for the maintenance doses. This avoids the stimulating effects of large doses and makes prolonged hormonal therapy more satisfactory. The slower antirheumatic response to small doses is more acceptable to us than the difficulties resulting from prolonged use of doses in excess of the anticipated tolerance. In our experience the highest maintenance dose of cortisone tolerated by postmenopausal women is approximately 25 to 30 mg. a day, by premenopausal women 35 to 40 mg. a day, and by adult men 40 to 50 mg. a day. Generally these are upper limits; we like to keep below these maximal doses, whether it is the first or hundredth day of treatment.

Use of corticotropin "to stimulate the adrenal cortex" of a patient with chronic hypercortisonism while the excessive dose of cortisone is being decreased may apparently improve symptoms of the mesenchymal reaction, but this is only a temporary effect when it occurs. The addition of corticotropin may thus perpetuate rather than correct the state of hypercortisonism. Very gradual decreases of hormonal dosage with discontinuation of hormonal therapy if necessary has so far been the most reliable long-term approach to the correction of chronic hormonal overdosage.

Treatment of Systemic Lupus Erythematosus with Prednisone and Prednisolone. By ALFRED JAY BOLLET, STANTON SEGAL, and JOSEPH J. BUNIM, *Bethesda, Md.*

Ten patients with systemic lupus erythematosus, in whom the disease was not satisfactorily controlled by cortisone, hydrocortisone, corticotropin, or combinations of these hormones, were given prednisone (metacortandracin) or prednisolone (metacortandralone) after a suitable period of control observation. The initial suppressive dose varied between 20 and 60 mg. per day, and the minimum maintenance dose between 5 and 30 mg. per day. These drugs were found to be approximately four times more potent than the other steroids, and no difference was noted between prednisone and prednisolone. The synthetic steroids were very effective in suppressing the systemic manifestations of lupus, such as chills, fever, and malaise; skin and mucous membrane lesions healed, and leucopenia improved. The anaemia was not usually altered, and the L.E. phenomenon persisted. The C-reactive protein when present disappeared on therapy, and the sedimentation rate decreased, but did not usually become normal. Pulmonary and pleural changes were rapidly reversed, although patches of rales occasionally persisted. Cardiac murmurs and pericardial friction rubs improved, but enlargement of the heart and E.C.G. abnormalities did not. Azotaemia and urinary abnormalities receded only when they had previously been aggravated by systemic toxicity or other extrarenal factors. In patients with nephrotic syndrome, no alteration in protein excretion occurred. No improvement in electrolyte abnormalities (*e.g.*, hyponatraemia and hyperkalaemia) occurred on treatment, and no alterations in blood pressure were noted either in the three hypertensive patients, or in those with normal tension. Retinopathy cleared in one of three instances. Serum albumin levels increased slightly on treatment in most patients, but did not return to normal in any; elevated serum globulin levels, which were present in six patients, decreased slightly in some but did not return to normal. Oedema, which was present in three patients, diminished in all, but disappeared completely in only one. Convulsions and mental changes apparently due to "lupus" lesions in the central nervous system were improved, but E.E.G. abnormalities were not altered. In general, these patients were somewhat better on maintenance doses of prednisone than on previous steroids, and no serious side-effects were noted.

Discussion.—DR. CHARLES LEROY STEINBERG (*Rochester, N.Y.*): Lupus erythematosus is a disease with many systemic manifestations, and the evaluation of the effect of any drug on the clinical course of such a complex disease becomes difficult.

In general, our conclusions are the same as those given by Dr. Bollet and his group. We have had the opportunity of treating seven patients with systemic lupus and three patients with periarteritis nodosa with prednisone. The effect on the cholesterol in some of these patients was interesting and complex. Renal manifestations are frequent in systemic lupus, and in some of our patients the cholesterols and cholesterol esters rose while they were under metacortandracin therapy.

The question arose whether we had aggravated a renal lesion such as have been stated to occur when cortisone and corticotropin were first tried in this disease, but we found that neither the azotaemic level nor the urinary findings followed the cholesterol level.

One patient with periarteritis nodosa died while under treatment. The autopsy showed most extensive arterial involvement, both visceral and peripheral, and a remarkable feature was that the histological studies showed no inflammatory process in the diseased arteries, the inference being that, if this patient had been treated earlier, the outcome would have been favourable. Two other patients with periarteritis nodosa have been converted from very sick to employable.

The seven patients with L.E. had previously been treated with either cortisone or corticotropin, and all have done very well with prednisone, but in no instance did the L.E. cells disappear from the bone marrow or the peripheral blood. In one instance in which the white blood count was as low as 1,300 on 150 mg. cortisone daily, it rose to normal on prednisone and has remained so for several months.

All seven patients carry on their usual activities with little or no restriction, and can tolerate a normal diet with no salt restriction or doses of potassium.

The initial dose used was 30 mg. per day, and except the individual who died with periarteritis nodosa, these patients have had nearly 4 months' observation. The

dose was decreased by 5 mg. every 5 days until the least amount required for maintenance was reached, usually in the region of 15 to 20 mg. per day. We have not been able to reduce our dosage to as low as 5 mg.

DR. GERALD P. RODNAN (*Bethesda, Md.*): We have used prednisone in six patients with progressive systemic sclerosis. There were four women and two men in this series, and the duration of the illness ranged from 1½ to 6½ years. In addition to widespread cutaneous disease, they all presented involvement of at least one other system. Subcutaneous calcinosis was clinically and/or roentgenographically demonstrable in three. In three there was frank polyarthritis, particularly in the hands and knees, the sheep cell agglutinin titres were 4, 16, and 32. Clinical and/or radiological evidence of oesophageal involvement was present in five. In one woman there were symptoms referable to small bowel disease, and *x* rays demonstrated marked abnormalities in gut motility and mucosal pattern. One 60-year-old male, much troubled with exertional dyspnoea, was found to have an enlarged heart, reticular pulmonary fibrosis, and an abnormal electrocardiogram.

Skin biopsy in each instance confirmed the impression of scleroderma. In those patients with arthritis, synovial biopsy revealed acute or chronic synovitis, characterized by infiltrates of lymphocytes and plasma cells, with focal fibrosis.

A base-line observation period of approximately one month was obtained, when serial review of symptoms and physical findings was made. Following a course of placebo medication, the patients received prednisone, 30 mg. per day in divided doses orally. While on medication, the patients had 3 g. sodium per day.

The most dramatic response to this treatment was observed in those patients with joint involvement. Within 48 hours they noted marked alleviation of pain and stiffness. This improvement continued and has persisted for up to 4 months on therapy. Changes in the skin were evident usually within a week, with diminution in the tightness, oedema, and hyperpigmentation. Skin previously stretched taut could be wrinkled. Only slight change was noted in those areas in which the skin had undergone marked atrophy.

The patient with cardio-pulmonary disease experienced considerable improvement in his dyspnoea and pulmonary function studies demonstrated a marked increase in maximal breathing capacity. The electrocardiogram and chest film remained unchanged. The woman with small bowel difficulty continued to have considerable distress, with gaseous distention and motility disturbances.

There was an increase in haematocrit and a fall in erythrocyte sedimentation rate and C-reactive protein. The eosinophil counts were reduced sharply. With few exceptions, changes in the serum protein level were slight and of questionable significance.

No changes were apparent in *x* rays of the joints and gastro-intestinal tract or in the appearance of skin and synovial biopsies obtained after a month or more.

Side-effects were minimal, apart from the occasional development of mild facial rounding and acne. Blood pressure remained normal and there was no fluid retention.

Observations on Prolonged Administration of Metacortandracin in Rheumatoid Arthritis. By ROGER L. BLACK, ALFRED J. BOLLET, STANTON SEGAL, and JOSEPH J. BUNIM, *Bethesda, Md.*

Eighteen patients with active, progressive rheumatoid arthritis who had failed to respond satisfactorily to aspirin, gold compounds, cortisone, hydrocortisone, corticotropin or phenylbutazone, and who exhibited in most instances striking improvement when given metacortandralone or metacortandracin, received the new steroid for periods varying from 6 to 10 months.

The adrenal cortical function was suppressed and undesirable side-effects occurred, including facial rounding, diminished carbohydrate tolerance, duodenal ulcer formation, and mental disturbance. In some patients the maintenance dose had to be increased to sustain the improvement initially achieved.

The early impression has been confirmed that the new steroids are four times more potent than cortisone or hydrocortisone and that when reversible changes are present maximal rather than "suboptimal" improvement can usually be attained without increased hazard.

Discussion.—DR. C. PLOTZ (*New York City*): We owe Dr. Bunim and his group a debt for their pioneer work with this new hormone.

We all have to share the blame for the interval between the favourable report and the reports of toxic reactions; six weeks ago in a report on over 1,000 patients, the incidence of side-reactions was only about 11 per cent., and this is clearly due to a lag in reporting these side-reactions to the manufacturers.

We have used this hormone in 42 patients; two developed peptic ulcers and one acute thrombophlebitis, in one an old fibrotic pulmonary lesion became active, one became severely depressed and made an unsuccessful attempt at suicide, and one with psoriasis and rheumatoid arthritis who had previously been controlled successfully on ACTH and on cortisone had a severe exacerbation of her psoriasis though the arthritis was controlled.

The last patient in whom we had to discontinue treatment with metacortandracin was quite unusual. She had an undiagnosed mesenchymal disease, possibly lupus, about 50 per cent. diminution in renal function. She was put on prednisone in doses of 20 to 30 mg. daily for 4 weeks, but the hormone had to be discontinued because she had gained 11 lb. of oedema fluid.

DR. WILLIAM H. KAMMERER (*New York City*): Our experience with Meticorten (metacortandracin) dates from Nov., 1954, since when we have observed its effects in 96 patients; 76 had rheumatoid arthritis; and 44 have now been under observation for 3 to 6 months. A great many have now been put into Grade I and II and Classes I and II; this appears impressive, but does not tell the whole story, for many of them had been on intra-articular hydrocortisone at varying intervals; some had had Butazolidin as an analgesic agent, and all were receiving a substantial amount of salicylates. Since prednisone therapy was begun, many of these added measures have been discontinued.

Out of 41 patients on long-term steroid therapy, many went from Grade III and IV on cortisone and hydrocortisone to Grade I and II on prednisone, and I think we must agree that prednisone is a better antirheumatic agent than cortisone and hydrocortisone, but we do not know what the long-term effect of prednisone in the treatment of rheumatoid arthritis will be, and we probably shall not have the answer for 2 or 3 years. In the past 2 or 3 weeks, several patients who had been on prednisone therapy for 4 to 6 months have begun to have a flare in activity while continuing with the dosage which had previously controlled their symptoms. It may be that long-continued therapy will result in the "petering

out", as Dr. Cecil describes it, of the antirheumatic effect, but only time will tell.

With regard to calcium metabolism and the possible occurrence of peptic ulceration, in our group of 96 patients we discontinued prednisone in three: in one because of radiologically proven gastric ulcer, in one because of symptomatology of peptic ulcer, and in one because of phlebitis. These side-effects do occur, but we should not magnify them out of proportion. I agree with Dr. Plotz that mooning and other minor side-effects may be somewhat more prominent, but though they are undesirable there is no solution for them. The patient must accept either the minor side-effect or the rheumatoid arthritis.

Comparison of the Metabolic Effects of Prednisone and Cortisone. By EVAN CALKINS, LEON REZNICK, and WALTER BAUER, *Boston, Mass.*

In order to study the many variables influencing calcium, nitrogen, and phosphorus metabolism in rheumatoid arthritis, a patient was selected with disabling dermatitis, confined to the finger tips and not accompanied by systemic manifestations, and 12-day periods of therapy with prednisone (Meticorten) and prednisolone (Meticortelone) in oral doses of 75 mg. daily, were compared with a 12-day period of treatment with 300 mg. cortisone daily. Control periods of 12 or 16 days intervened between treatments. Both prednisone and prednisolone caused losses of nitrogen (4 g./24 hr) and phosphorus (0·3 g./24 hr). Cortisone caused much smaller losses (0·5 g. nitrogen and 0·05 g. phosphorus). Both prednisone and cortisone caused an increase in urinary calcium excretion (0·03 g./24 hr).

Five patients with pemphigus vulgaris were treated with prednisone, 80-120 mg. per day. All displayed alterations in carbohydrate metabolism as great as or greater than previously observed with cortisone or ACTH. This consisted in one or more of the following: marked abnormalities in glucose tolerance, elevation in blood sugar (as high as 300 mg. daily), glycosuria (as high as 100 g./24 hr), and marked elevation in plasma lactate and serum pyruvate both while fasting and during the glucose tolerance test.

This data, in agreement with recent evidence from other clinics, indicates that, in comparison with cortisone, prednisone exhibits, milligram for milligram, greatly enhanced metabolic as well as antirheumatic effects.

Discussion.—DR. CARL STEVENSON (*New York City*): Hyperglycaemic effects of cortisone acetate, hydrocortisone acetate, and prednisone were studied in a 53-year-old female patient with rheumatoid arthritis. The unexpected finding of glycosuria during a previous short course of cortisone prompted the investigation.

A moderate disturbance of carbohydrate metabolism was present when the cortisone was administered, manifested by a fasting blood sugar of 168 mg./100 ml. This was later shown to be a residual effect of the previous, short period of cortisone administration which ended 18 days before this study began. The initial dose of cortisone was 200 mg. daily, with later doses of 150 and then 100 mg. daily (Figure, overleaf).

Large doses of cortisone were continued despite evidence of severe disturbance of glucose metabolism, since ketosis, acidosis, and weight loss did not occur, and because the patient continued to feel well. The hormone was discontinued after 75 days of administration, and after 115 days of no medication the glucose tolerance had reverted almost to normal. (The fasting blood sugar was normal; the peak value of blood sugar during a glucose tolerance was 192 mg./100 ml.)

Hydrocortisone acetate was then injected intramuscularly in doses of 100 mg. daily. The glucose tolerance was noted to change significantly on the 15th day; the fasting blood sugar became elevated between the 25th and 35th days. Again, no other adverse effects were noted. After the cortico-steroid was discontinued there was gradual improvement of carbohydrate metabolism; the glucose tolerance was normal 180 days later.

Three years later this patient participated in a similar study of prednisone. Several pre-treatment glucose tolerance tests revealed a persistent, mild asymptomatic diabetic state. Fasting blood sugar values ranged from 100 to 120 mg./100 ml. with peak tolerance values up to 220 mg./110 ml.

The initial dose of prednisone was 40 mg. daily. Between the 15th and 35th day a steroid-induced diabetic effect similar to that with cortisone and hydrocortisone was noted. After the drug was discontinued this state began to improve, and the pre-prednisone status was attained in about 120 days.

This patient developed a temporary severe carbohydrate metabolic disturbance when treated with cortisone acetate, hydrocortisone acetate, and prednisone. These results indicate similar "diabeticogenic" effects from all three of these cortico-steroids.

* * * *

PANEL DISCUSSION

(MODERATOR: DR. J. J. BUNIM)

Newer Analogues of Adrenocortical Steroids

(see Table, overleaf)

Biosynthesis and Metabolism of Adrenocortical Hormones. By RALPH I. DORFMAN, *Shrewsbury, Mass.*

The adrenal cortex produces a variety of steroid hormones under the influence of adrenocorticotropic hormone (ACTH). The action of ACTH seems to be threefold:

(A) the growth of all the cortical elements, which probably occurs in a matter of days;
(B) the formation of specific biosynthetic enzymes, which probably occurs in hours;
(C) a direct action on the biosynthetic mechanisms which occurs in minutes.

On the basis of the best evidence, biosynthetic reactions in the adrenal may be considered to start from acetate and cholesterol and proceed by two independent reaction sequences to the corticoids (C_{21} steroids) and to the androgens (C_{19} steroids). The formation of a substance such as cortisol (hydrocortisone) proceeds from acetate and cholesterol by way of pregnenolone to progesterone. Progesterone is hydroxylated at carbons 11, 17, and 21. Thus, six hydroxylated intermediates are formed which in turn may be converted to cortisol. Aldosterone

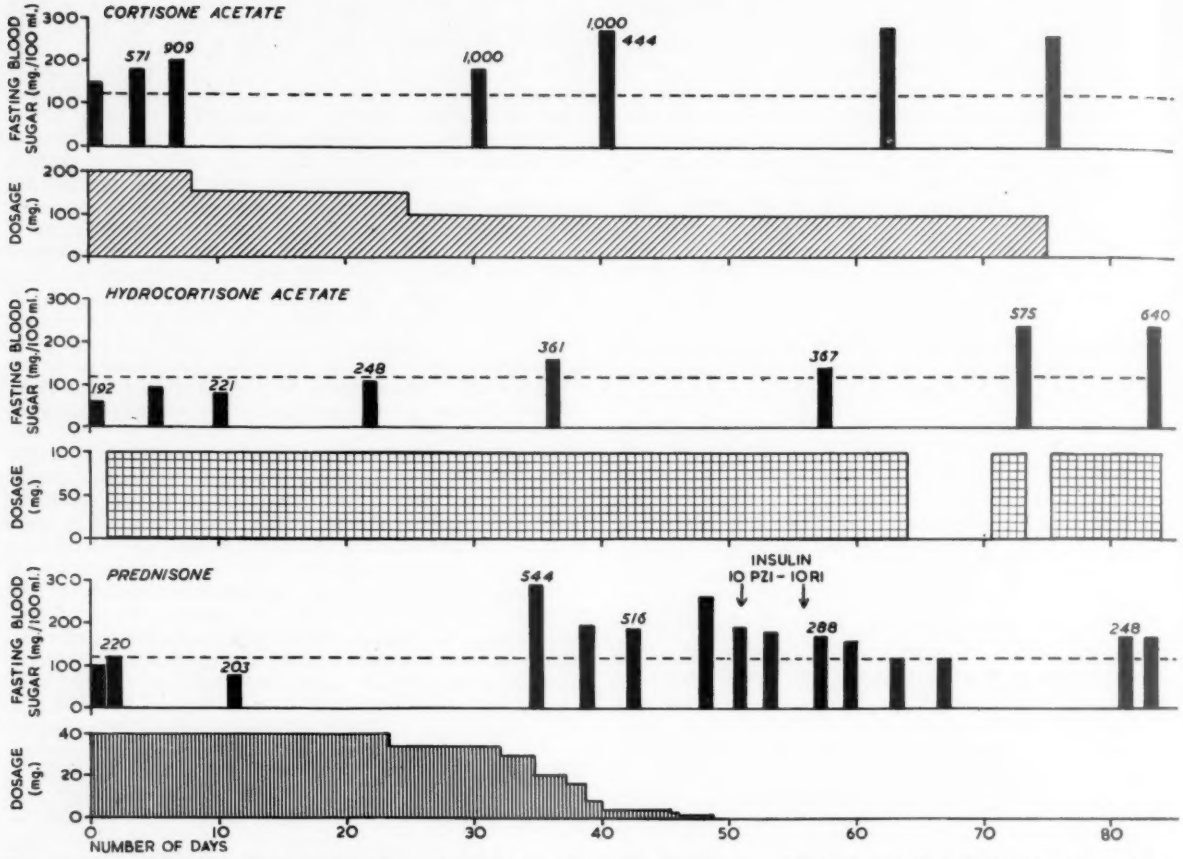


Figure.—Alterations of blood sugar produced by cortisone, hydrocortisone, and prednisone. Vertical bars indicate fasting blood sugar (mg./100 ml.). Figures above some of the bars represent peak blood-sugar values on a 100-g. oral glucose tolerance test.

appears to be biosynthesized by way of progesterone, desoxycorticosterone and 18-hydroxydesoxycorticosterone. The biosynthesis of androgens proceeds from acetate and cholesterol to dehydroepiandrosterone, then to Δ^4-androstene-3, 17-dione, and finally to 11β-hydroxy-Δ^4-androstene-3, 17-dione.

The various adrenocortical steroids are secreted into the blood and catabolized by a variety of enzyme systems in the liver, kidneys, and other organs. The known catabolic changes involve reductive changes at various positions of the steroid molecule such as at carbon 3, 4, 5, and 20, and the oxidative removal of the side chain in some C_{21} steroids forming C_{19} steroids. These products are present in the urine.

MODERATOR BUNIM: To the classical examples of disorders resulting from the presence of C_{21} or C_{19} steroid-secreting tumours in the adrenal cortex which Dr. Dorfman has so clearly described, may now be added a new syndrome, aldosteronism, recently described by Jerome Conn. It is characterized by alkalosis with hypopotassaemia and hypernatraemia, intermittent tetany, muscular weakness, hypertension, and polyuria. There is an excess of aldosterone-like material in the urine, yet the 17-hydroxycorticoid excretion is either normal or only slightly raised. It is believed that this syndrome is associated with adrenal tumours which secrete excessive amounts of aldosterone.

Relation of Chemical Structure to Biological Activity of Adrenal Cortical Steroids including the Halogenated Analogues. By JOSEF FRIED, *New Brunswick, N.J.*

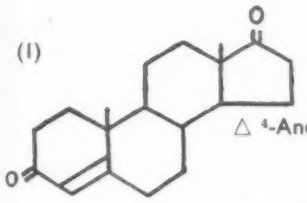
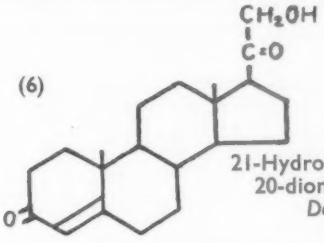
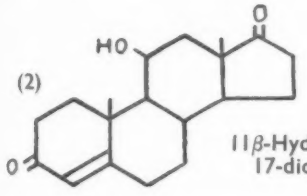
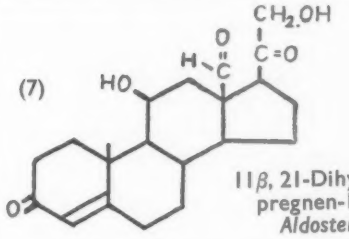
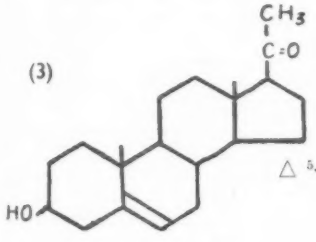
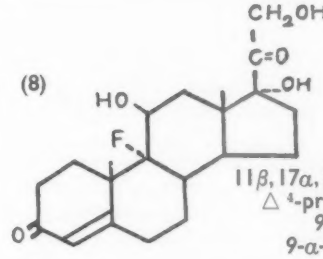
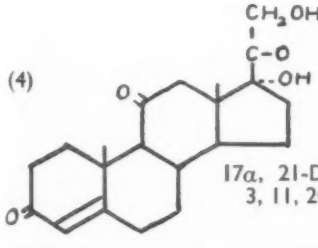
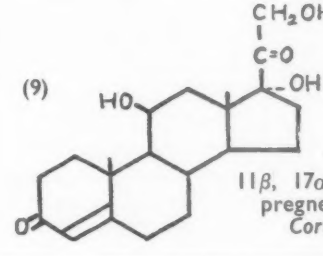
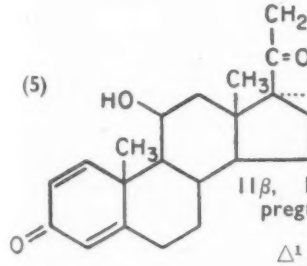
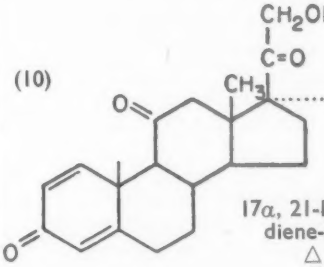
Efforts to enhance the antirheumatic activity and minimize the undesirable side-effects of cortisone and hydrocortisone by modifying the molecular structure of these hormones have until recently met with little success. The conclusion seemed warranted that the structural requirements for an active compound were too exacting to permit chemical modification of the naturally-occurring hormones without complete or partial loss of activity.

The discovery that the introduction of a chlorine and particularly a fluorine atom in the 9-α position of cortisone and hydrocortisone leads to increases in glucocorticoid (cortisone-like), mineralocorticoid (aldosterone-like), and anti-inflammatory activity has made it possible to evaluate the influence of structural changes on the various manifestations of corticoid activity.

The compounds studied by us differ from hydrocortisone and cortisone by the presence of a halogen atom (bromine, chlorine, and fluorine) in the 9-α position, and

TABLE

Nomenclature and Structure of Some Adrenocortical Steroids and Related Steroids

STEROID STRUCTURE	SYSTEMATIC NAME (Common Name)	STEROID STRUCTURE	SYSTEMATIC NAME (Common Name)
(1) 	△ 4-Androstene-3, 17-dione	(6) 	21-Hydroxy-△ 4-pregnene-3, 20-dione *Desoxycorticosterone*
(2) 	11β-Hydroxy-△ 4-androstene-3, 17-dione	(7) 	11β, 21-Dihydroxy-3, 20-keto-△ 4-pregnen-18-al *Aldosterone; Electrocortin*
(3) 	△ 5-pregnene-3β-ol-20-one *Pregnenolone*	(8) 	11β, 17α, 21-Trihydroxy-9α-fluoro-△ 4-pregnene-3, 20-dione *9-α-fluoro cortisol; 9-α-fluoro hydrocortisone*
(4) 	17α, 21-Dihydroxy-△ 4-pregnene-3, 11, 20-trione *Cortisone*	(9) 	11β, 17α, 21-Trihydroxy-△ 4-pregnene-3, 20-dione *Cortisol; Hydrocortisone*
(5) 	11β, 17α, 21-Trihydroxy-△ 1, 4-pregnadiene-3, 20-dione △ 1 *-Dehydrocortisol; △ 1 Dehydrohydrocortisone; "Metacortandralone"; Prednisolone*	(10) 	17α, 21-Dihydroxy-△ 1, 4-pregnadiene-3, 11, 20-trione △ 1 *-Dehydrocortisone; "Metacortandracin"; Prednisone*

possess side chains varying in their degree of hydroxylation. The following generalizations concerning the relationship between chemical structure and biological activity can be made:

(1) Lowering the atomic weight of the halogen atom leads in all the cases examined to increased glucocorticoid, anti-inflammatory, and mineralocorticoid activity;
(2) In the fluorinated derivatives, substitution of a hydroxyl group for a hydrogen atom in position 21 leads to increases in glucocorticoid, anti-inflammatory, and mineralocorticoid activity. Hydroxylation in the 17-α position causes increases in the first two types of activity and a decrease in the last.

The most active compound of this series, 9-α-fluoro hydrocortisone, possesses ten to fifteen times the anti-inflammatory activity of hydrocortisone. Its high sodium-retaining activity precludes its systemic use in rheumatoid arthritis but not its topical use in dermatology. The fact that specific chemical groupings can cause enhancement of anti-inflammatory and reduction of salt-retaining action points to more potent and less toxic antirheumatic drugs in the future. The meta-drugs (1,2-dehydrocortisone and 1,2 dehydrohydrocortisone) appear to offer the first step in that direction.

Pharmacology and Rate of Metabolism of Hydrocortisone, Cortisone, and Metacortandracin, and the Rate of Synthesis of Hydrocortisone in Man. By RALPH E. PETERSON, *Bethesda, Md.*

We have measured the rate of metabolic transformation of both pharmacological and tracer (Carbon-^{14} labelled) quantities of intravenously administered hydrocortisone, by determining plasma concentrations at several time-intervals after injection. In normal subjects the biologic half-life of this steroid has been found to range from 1½ to 2 hours. The rate of metabolism has been found to be decreased in liver disease, and increased in thyrotoxicosis.

Similar studies have been carried out using cortisone and metacortandracin. Cortisone has been found to be metabolized twice as fast as hydrocortisone and metacortandracin. Data on the rate of excretion of infused hydrocortisone also demonstrates the rapid biotransformation (reduction and conjugation), with 50 per cent. excreted in 3½ hours. The urine contains 80 per cent. of the hydrocortisone metabolites within the first 24 hours, and more than 90 per cent. within the first 3 days. Biliary excretion accounts for but 4 per cent., and more than half of this quantity is eventually excreted in the faeces. More than 99 per cent. of the administered hydrocortisone is transformed by the body to metabolites other than hydrocortisone. Using hydrocortisone 4-C^{14}, we have measured the rate of synthesis of hydrocortisone by the adrenal glands. In normal subjects the adrenal glands produce about 20 mg. hydrocortisone per day. After maximal stimulation with ACTH, the adrenal output was increased approximately ten-fold. In both liver disease and myxoedema the adrenal output was decreased. As part of this same study on steroid production, the miscible pool of hydrocortisone was determined. In the normal it was about 2 mg., distributed in a space slightly larger than the volume of the extracellular fluid.

Effects of Aldosterone, 9-α-Fluoro Hydrocortisone Acetate and Metacortandracin on Rheumatoid Arthritis. By CHARLES H. SLOCUMB, L. EMMERSON WARD, HOWARD F. POLLEY, and PHILIP S. HENCH, *Rochester, Minn.*

Aldosterone was administered to two rheumatoid patients for six days each, in doses up to 800 μg. per day in one patient and 1,000 μg. per day in the other. These doses produced no antirheumatic effects, but did produce retention of sodium, chloride, and fluid.

9-α-fluoro hydrocortisone acetate was administered to three rheumatoid patients in doses up to 4, 6, and 8 mg. daily for 12 to 28 days. These comparatively small doses lessened rheumatic symptoms, but produced troublesome retention of sodium chloride and fluid, and loss of potassium. The changes were sufficient to cause oedema and hypopotassaemia with a tendency for the development of hypochloraemia and alkalosis.

Metacortandracin was administered to two patients for up to 24 days in dosages of up to 30 mg. a day. This dosage lessened rheumatic symptoms, and there was no significant excess sodium or chloride retention or potassium loss, although the patients were in negative nitrogen balance.

MODERATOR BUNIM: The next and last panellist is Dr. Edward Boland, whose presidential address forms part of this survey of progress in the development and trial of these steroids and their analogues.

Preliminary Clinical Experience with Metacortandracin in Rheumatoid Arthritis. By EDWARD W. BOLAND, *Los Angeles, Calif.*

Clinical observations were made of the effects of metacortandracin (Δ^1-dehydrocortisone) in 52 patients with active peripheral rheumatoid arthritis, treated uninterruptedly for periods of 3 to 5 months. The study, which is still in progress, was designed to determine:

(1) The effects of the compound when given as initial therapy;
(2) Dosage schemes for its practical application;
(3) The relative antirheumatic potencies of metacortandracin and hydrocortisone;
(4) The therapeutic efficiency of metacortandracin as compared to that of hydrocortisone on continued administration.

Group 1.—The response to metacortandracin employed as initial therapy was observed in eleven patients. Suppressive doses were varied with the severity of the disease and ranged from 15 to 30 mg. a day. Prompt and striking antirheumatic effects resulted in ten patients, the pattern of improvement being similar to that noted with hydrocortisone and cortisone given in larger suppressive amounts. Subjective relief began within 3 to 72 hours of the first divided dose, and objective improvement was noted within 2 to 7 days. Adequate suppression of the disease was achieved in nine patients after 7 to 21 days of administration. With daily main-

tenance doses ranging from 7·5 to 25 mg., major improvement was maintained for 3 to 5 months in nine patients. One or more adverse signs appeared in seven patients; these were minor in five, but sufficient in the other two to cause limitation of dosage below optimally effective levels.

Group 2.—Estimates were made of differences in antirheumatic potency between metacortandracin and hydrocortisone in fourteen patients. This was accomplished by transferring patients whose disease was adequately, but not completely, controlled on established stable maintenance doses of hydrocortisone to treatment with the new compound. In each instance the dosage of metacortandracin required to maintain approximately an equivalent degree of improvement was smaller. Dosage ratios of metacortandracin to hydrocortisone varied from 2·4 : 1 to 5·3 : 1 (average 3·97 : 1). Later the dosage of metacortandracin was increased above equivalently effective amounts, and in thirteen of the fourteen patients greater benefits were provided and maintained.

Group 3.—27 patients whose clinical control was unsatisfactory while being maintained on hydrocortisone, were transferred to treatment with metacortandracin. In 25 the immediate results were favourable; major improvement was achieved or restored with smaller, but more effective, doses of the new steroid.

After 3 to 5 months of continuous metacortandracin therapy, sixteen of the 27 patients (59 per cent.) were classified as adequately improved. In general, the percentage of patients demonstrating satisfactory control fell as treatment was prolonged: improvement was considered as adequate in 74 per cent. after 1 month, in 89 per cent. after 2 months, in 78 per cent. after 3 months, in 58 per cent. after 4 months, and in 50 per cent. after 5 months. Nine patients responded well at the beginning, but later deteriorated because responsiveness to the drug diminished and because side-effects intervened to a degree which forbade further increases in dosage. The dosages of metacortandracin varied from 7·5 to 30 mg. a day (average 16·7 mg.).

24 patients exhibited one or more hormonal complications, total 87 effects. After 3 to 5 months all 27 displayed unwanted reactions, total 94 effects. 27 side-effects disappeared, eight lessened in degree, 24 remained unchanged, and 28 became more pronounced. 34 "new" signs developed during administration of the new analogue, many of which were cumulative. Although most of these reactions were mild or moderate in severity, they were troublesome enough in ten patients to limit dosage and prevent satisfactory results.

These short-term observations indicate that metacortandracin has certain advantages over hydrocortisone in the treatment of rheumatoid arthritis, consisting mainly in the absence of salt-and-water retention with ordinary therapeutic doses, the capacity to restore adequate improvement in patients who have lost satisfactory control after prolonged hydrocortisone administration, and the ability to maintain the greater benefits in a significant percentage of such patients for periods up to 5 months, at least. However, the other difficulties and potential hazards encountered with the older steroids seem to be shared by the new derivative. Indeed, some adverse reactions, notably digestive complications, ecchymotic skin lesions, and vasomotor symptoms, have occurred more frequently and have been more troublesome with the new analogue.

Metacortandracin is thus, far from an ideal suppressive agent for rheumatoid arthritis, but it possesses some important refinements—and its discovery strengthens our conviction that, through further permutations of chemical structure, steroids with higher therapeutic efficiency may be developed in the future.

MODERATOR BUNIM: I will take the liberty of paraphrasing an especially lengthy question:

What is Dr. Dorfman's opinion of the comparative merits of different methods of measuring the relative potency of the biologically active steroids?:

(1) Its inhibitory effect on the pituitary as reflected by the reduction of 17-hydroxy steroids in the urine; by a decrease in the 17-ketosteroids in the urine; and by a decrease in the 17-hydroxycorticosteroids in the blood or plasmas;
(2) Its suppression of the endogenous production of hydrocortisone by the adrenal cortex as measured by the method described by Dr. Peterson.

DR. DORFMAN: Inherent in the question is the idea that there may be a correlation between the activities of a steroid by the different procedures named. If we are going to talk about relative merits we must ask if the different methods measure comparable activity, and it is doubtful whether this is so. Let us first consider pituitary inhibition and urinary steroids. Since 17-ketosteroid and 17-hydroxycorticoid (and I presume that the speaker is referring to the tetrahydro derivatives of cortisol and cortisone) excretion in urine is not always correlated under all physiological and pathological conditions, it would be presumptuous to assume, without adequate studies, that a correlation need exist. In short, one cannot choose between the indices, one can only suggest more studies whereby the various compounds are studied under comparable conditions by all the methods mentioned and perhaps even others.

MODERATOR BUNIM: Another question, sent to Dr. Fried, read something like this:

What would give you the best or the most reliable and direct correlation between the anti-inflammatory effects of a steroid and the following physiological tests:

(1) glycogenic deposition in the adrenalectomized rat;
(2) thymic involution;
(3) eosinophilic response;
(4) direct anti-inflammatory effect by cotton pellets in the rat?

DR. FRIED: We have used these four methods and I would say the quantitative correlation is about equally good for all of them with the exception of the thymic involution assay, which appears to be less specific. There are a number of substances that will cause thymic involution, but will not show liver glycogen deposition. The liver-glycogen test in the rat is a very accurate and economical test if properly carried out, and so is the cotton-pellet test for anti-inflammatory activity. We like these two methods, and so far the correlation is good.

Unfortunately, we do not know the antirheumatic activities in man of all the more active steroids discussed here and it would be very desirable, although some of these compounds may have undesirable side-effects, to

test them for their anti-arthritic effects, and to find out whether the correlation established in experimental animals is the same in man. Of the limited number of compounds that have been tested for their anti-arthritic activity in man, both the liver glycogen and the anti-inflammatory activity in the rat were paralleled.

MODERATOR BUNIM: Dr. Peterson, by the method of measuring the miscible pool and the rate of secretion of hydrocortisone, how does the potency of metacortandracic compare with that of hydrocortisone and cortisone; or did you not do those determinations?

DR. PETERSON: We have only done this in one case and with meticorten, so I have no data on the relative potency of the three steroids by this method.

MODERATOR BUNIM: Dr. Slocumb, please discuss briefly osteoporosis occurring in steroid administration.

DR. SLOCUMB: Dr. Bauer's group gave you more information than we have to-day. The short-term metabolic studies with these steroids have not given us a real answer as to the calcium metabolism compared with what we see clinically. Clinically, we feel that osteoporosis is produced by cortisone and hydrocortisone and undoubtedly by metacortandracin, but this comes after rather long administration and by adding to the tendency of the disease to produce osteoporosis.

The incidence of fractures, certainly of compression fractures, is certainly higher than we should expect in rheumatoid arthritics.

MODERATOR BUNIM: Should testosterone be used for its non-specific antibiotic effect in long-term therapy?

DR. SLOCUMB: I think it should be tried. It will certainly help with such things as nitrogen retention. We want to know about the appearance of all the side-effects of these hormones and are trying to find the safest way of administering them, so we are not adding testosterone, oestrogens, or the other things at this time.

MODERATOR BUNIM: Dr. Boland, is it necessary in the administration of metacortandracin: (*a*) to restrict sodium intake, (*b*) to supplement with potassium salts.

DR. BOLAND: Although metabolic studies performed by Dr. Bunim's group and by others indicated that metacortandracin in dosages of 30 mg. a day or less causes little or no alteration in sodium or potassium excretion, we approached the problem cautiously. Among our early patients extra salt, that is, amounts over and above that used normally in cooking, was denied. In later cases we became more liberal and at present most of our patients are on a regular diet and are not restricted in their salt intake. So far oedema resulting from salt retention has not been a problem, and we have found no need for complemental potassium salts or other diuretic agents.

MODERATOR BUNIM: Please compare metacortandracin and metacortandralone in simple application.

DR. BOLAND: We have now had experience with metacortandralone in well over 75 patients with rheumatoid arthritis. So far we can see little difference between metacortandralone and metacortandracin in regard to antirheumatic potency or adverse effects. The two substances have been found to be interchangeable, and differences, if they do exist, must be very small.

MODERATOR BUNIM: Here is a question which I cannot direct to any specific member of the panel. I am inclined to call on a volunteer from the audience: "May it not be possible that many of the ill effects and apparent inadequacies of the steroids may be due to an effect on the basic immune mechanism? If so, what future can be expected from this direction?"

DR. BOLAND: I doubt whether any member of the audience is bold enough to attempt to answer this!

MODERATOR BUNIM: Another question directed to Dr. Boland: "To reduce the side-effects of meticorten, is it advisable to combine 50 per cent. of hydrocortisone with 50 per cent. of Meticorten?"

DR. BOLAND: The practical management of patients with both hydrocortisone and metacortandracin is so complex that we have not had the temerity, nor have we seen reason, to use them in combination.

MODERATOR BUNIM: Another question for Dr. Slocumb: "What measure can you employ to counteract the decalcifying effects of corticosteroids?"

DR. SLOCUMB: We keep the dosage down and our patients ambulatory. We have not found it necessary, with the small dosage, to give calcium or aluminium salts.

If there is compression, we start gradual reduction, see that the back or area in question is properly supported, and get the patient active again as soon as we can, that is within a week or so.

DR. BOLAND: I should like to ask Dr. Fried and Dr. Dorfman together—and to get this answer was one of the objects of this symposium: Do you think it possible to develop a substance with antirheumatic activity and to get the bugs out and to get the side-effects out of it in the future? Dr. Fried?

DR. FRIED: Studies of the various hydrocortisone analogues show that some of the metabolic actions of hydrocortisone (such as its effects on carbohydrate, protein, lipid, and electrolyte metabolism) can be intensified or reduced independently of each other. In other words, a certain alteration in chemical structure may potentiate one metabolic effect, diminish another, and leave a third unaffected. This may be interpreted to mean that each metabolic effect has its own specific structural requirements.

Now if you accept that premise, you may justifiably conclude that it is theoretically possible to create a substance that causes only the effects that you require and none that you do not. More knowledge of the relationship between structure and activity is necessary.

DR. DORFMAN: Concerning the intensification of desirable properties and the minimizing of unfavourable properties in "tailor-made" steroids, we have recently seen very striking successes, not only in the separation of carbohydrate and protein activity from electrolyte effects, but even in modifications of the relative sodium and potassium effects in some of the newer compounds. If such divergencies can be produced, further effort may bring us closer to the realization of more ideal thera-

peutic agents. In this field, industry, through the efforts of workers like Dr. Fried, is showing us the way.

* * * *

FIVE PAPERS PRESENTED IN CONJUNCTION WITH THE AMERICAN COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

(1) Isolation and Characterization of the Non-Specific Hyaluronidase Inhibitor of Human Blood. By GERALD S. BERENSON, JOYCE K. NEWMAN, MARTIN B. MATHEWS, and ALBERT DORFMAN, *Chicago, Ill.*

Previous studies have demonstrated the presence of a substance in the blood of humans and other mammalian species which inhibits the enzyme hyaluronidase. One of the changes occurring in blood during the acute phase of rheumatic fever and other inflammatory conditions involve an increase in the level of the non-specific hyaluronidase inhibitor. The lability and its invariable presence, irrespective of a previous exposure to hyaluronidase, suggest that this substance differs from specific antibodies to hyaluronidase. More recently, attempts have been made to add to information concerning the nature of this substance. This report deals with the isolation and characterization of the inhibitor.

By means of a purification procedure (involving alcohol fractionation, precipitation at low ionic strength, and zone electrophoresis on a starch slab), a material with hyaluronidase inhibitory activity was isolated with a purification up to approximately 1,000-fold over plasma. Preparations so isolated appeared to be essentially monodisperse on ultracentrifugation, free solution electrophoresis, and diffusion studies. The molecular weight was calculated to be about 100,000. The sedimentation constant $S_{20} = 3{\cdot}7$ S and mobility in a veronal buffer, *p*H 8·6, $\mu 0{\cdot}1 = -5{\cdot}4 \times 10^{-5}$ cm.^{2} sec.$^{-1}$ volt.$^{-1}$ Chemical analysis showed the following composition (per cent.):

N	14·4
Polypeptide content	75
Hexosamine	4
S	< 0·1
P	0·2
Tyrosine	2·7
Tryptophane	0·9

A positive test for hexuronic acid was obtained by the carbazole method and a qualitative amino acid composition, by means of paper chromatography, indicated the presence of twelve to fourteen different amino acids.

(2) Immunological Evidence of Group A Streptococcal Infection in Patients undergoing Mitral Commissurotomy. By W. F. LYNCH, G. H. STOLLERMAN, M. A. DOLAN, D. YOUNG, and J. B. SCHWEDEL, *New York, N.Y.*

Forty-five patients undergoing mitral commissurotomy for mitral stenosis were studied to determine whether antecedent group A streptococcal infection was related to

(*a*) histological findings in the biopsied auricular appendage;

(*b*) the post-operative development of clinical manifestations suggesting reactivation of rheumatic fever.

Serial determinations of the serum titres of antistreptolysin O, antihyaluronidase, and antistreptokinase were made pre-operatively and each month during a post-operative period of at least 3 months. Throat cultures were made at monthly intervals in most cases, and wherever possible prophylaxis against intercurrent streptococcal infection was maintained.

Of the 45 patients studied, 36 were found to have low serum levels (below 200 units/ml.) of all three antibodies immediately before operation. Of these patients, in whom recent pre-operative streptococcal infection was not apparent, five were found to have characteristic Aschoff nodules in the biopsied auricular myocardium. In four others the histological findings were suggestive of rheumatic myocarditis. In nine, immunological evidence of recent streptococcal infection was found pre-operatively; of these, one had typical Aschoff nodules in the biopsied auricular appendage and two had lesions suggestive of rheumatic myocarditis.

Eight patients developed manifestations suggestive of the "post-commissurotomy syndrome". In two of these there was no immunological evidence of streptococcal infection pre- or post-operatively. In the remainder, three had high levels of antibodies before operation and three others showed a significant rise in antibody during the post-operative period before the onset of the post-commissurotomy syndrome.

The data indicate that Aschoff nodules may often persist in the myocardium without immunological evidence of recent streptococcal infection being obtained by the methods employed. It also appears, however, that streptococcal infection is relatively common post-operatively (it occurred in twelve of 45 patients) and may be among the factors influencing the post-operative course, particularly the reactivation of rheumatic fever.

Discussion.—DR. ARNOLD LIEBERMAN (*Northport, Long Island, N.Y.*): How long after surgery do you advocate continuing your prophylaxis?

DR. LYNCH: We did not determine that point; we arbitrarily took a period of 3 to 4 months after surgery, but have reached no conclusions on how long prophylaxis should be continued post-operatively.

(3) Changes in Serum Concentrations of the Enzyme, Glutamic Oxalacetic Transaminase, in Rheumatic Fever (Preliminary Report). By IRWIN NYDICK, JAMES TANG, GENE H. STOLLERMAN, FELIX WROBLEWSKI, and JOHN S. LA DUE, *New York, N.Y.*

A simple, accurate, spectrophotometric test for the analysis of the serum concentration of the enzyme, glutamic oxalacetic transaminase (SGO-T) has been previously devised. Studies have shown this enzyme to be most concentrated in heart muscle and to rise precipitously in the serum following myocardial necrosis in man and experimental animals. The theoretical and clinical importance of testing for necrosis of the myocardial fibre, *per se*, in rheumatic fever is the basis of the present study of 64 rheumatic subjects in all stages of the

disease. Of 26 patients with active carditis, seventeen were found with abnormal serum levels; of eighteen "inactive" patients with a definite recent or past history of carditis, all sera analysed were within normal limits. Of twelve patients with non-cardiac rheumatic manifestations, only one developed abnormal serum concentrations of SGO-T, and this patient subsequently developed equivocal signs of an active carditis. Eight rheumatic subjects who developed virus pneumonia were studied, and in one an evanescent, slight elevation of SGO-T occurred when the EKG showed grossly abnormal T-waves, probably the result of the mild myocarditis occasionally seen with virus pneumonia.

There was no obvious relationship of the SGO-T to levels of the various "acute phase reactants". When the erythrocyte sedimentation rate, C-reactive protein, and white blood count were normal during antirheumatic therapy, there were often striking rises in SGO-T. The clinical course of carditis did not consistently parallel fluctuations in the enzyme levels. Some patients with severe carditis and congestive heart failure had normal levels; others with low-grade carditis were seen with five-fold increases. Aspirin and steroid therapy had variable relationships to changes in the SGO-T.

A microscopic study of auricular appendages (operative specimens) was undertaken in twelve patients and tissue obtained at autopsy was available in three. The SGO-T was abnormal at some time in five or ten patients with at least one of the following microscopic signs of inflammation: Aschoff nodules, round-cell infiltrations, acute myocardial cell necrosis, fibrinoid degeneration of collagen. Of the five patients with no microscopic evidence of inflammation, only one showed an elevation of the SGO-T, and in this patient extensive fibrous replacement of myocardial fibres was seen at autopsy.

Discussion.—DR. JOHN H. VAUGHAN (*Richmond, Va.*): Is there definite evidence that skeletal muscle wasting, such as one sees in chronically ill patients merely lying in bed, does not elevate the SGO-T, and more particularly whether this might not occur in muscle-wasting myopathies such as thyrotoxic or rheumatoid myopathy.

I gather that it is your impression that, though infractions of the liver may give rise to elevated SGO-T, this does not occur in acute passive liver congestion.

DR. NYDICK: We studied a large number of chronically debilitated patients with generalized carcinoma at the Memorial Hospital. Muscle wasting is often a prominent feature of their disease. In general, these patients did not have transaminase elevations unless the liver was involved by metastases.

We studied SGO-T levels in degenerative myopathies but did not follow the course of the transaminase over long periods; those that we followed for a few days to a few weeks were normal, but during the active phase of dermatomyositis in two patients, elevations of the transaminase occurred, which were presumably due to acute skeletal muscle necrosis.

Two patients with marked thyrotoxicosis had normal transaminase activity although they had clinical and laboratory evidence of severe thyrotoxicosis associated with marked muscle weakness; 28 patients with passive congestion of the liver failed to develop increased SGO-T. In two of these latter, moderate elevations were noted in acute shock-like episodes in the course of the congestive failure. These may have reflected liver injury due to anoxaemia and were perhaps caused by areas of hepatocellular necrosis such as have been reported after shock.

DR. HARRY A. FELDMAN (*Syracuse, N.Y.*): The authors were wise to label this a preliminary report, because it appears that this problem requires a good deal more study. In recent weeks, Dr. Lionel Rudolph of our department has measured the serum transaminase content of five patients with acute rheumatic fever and active carditis, and in only one of them was a level as high as 44 units found. This was in a patient who had two determinations; first 22 units and a week later 44, a change of only questionable significance.

One of the five patients died and was found to have gross evidence of acute rheumatic pancarditis at autopsy. She had had a level of 8 units 2 days before death. In the microscopic sections there is evidence of widespread myocardial involvement.

I have made some calculations from the data presented and it comes out that in the group with congestive failure and active carditis, some 19 per cent. of determinations—not patients—were abnormal.

In the group which was thought to have rheumatic heart disease and active rheumatic fever without carditis, 20 per cent. of the determinations were abnormal. In the group with polyarthritis (admittedly only one of these patients had any abnormal measurements), abnormal levels were encountered in 21 per cent. These three different clinical groups therefore show approximately similar frequencies of abnormal serum transaminase levels.

DR. NYDICK: In the five patients studied by Dr. Rudolph, very few serum glutamic oxalacetic transaminase determinations were done. I think that this is critical because in our group of patients, sera were obtained three times weekly, and it is obvious that the course of the serum transaminase may be very variable during rheumatic carditis, so that it would be easy to miss occasional peaks. For example, in two of the children it rose as high as 200 units, but had we skipped that particular week we should have missed the peak as well as the subsequent abnormal concentrations. It is essential to obtain sera frequently while studying the course of transaminase in rheumatic fever. Rheumatic fever is primarily an inflammatory process in collagenous tissue and the ground substance. It would be surprising if myocardial necrosis continued throughout the entire course of rheumatic carditis. It seems more likely (and this is what we should like to infer from our data) that during the course of the interstitial inflammatory process in the heart, myocardial necrosis may supervene; at that time the transaminase may rise and thus reflect the myocardial fibre involvement, not necessarily the interstitial inflammation.

We believe that our analysis of the percentage of abnormal results was valid for three reasons. First, 14 per cent. of the total number of determinations in the first two groups of patients ("definitely active carditis" and "questionably active carditis") were abnormal, as contrasted with 4 per cent. in all the other groups. Second, 65 per cent. of all the patients with carditis revealed abnormalities in the SGO-T at some time during their course as contrasted with the other groups, in which only 4 per cent. of the total developed elevations at any time. Finally, if one excludes the one patient with polyarthritis who was discussed in detail, and in whom equivocal evidence of carditis was present, only one

abnormal result was obtained in over three hundred sera analysed in the entire group of patients without known active carditis, *i.e.* convalescent rheumatic patients, patients with chorea, rheumatoid arthritis, erythema marginatum, and rheumatics who developed virus pneumonia. We believe that analysing the data in this fashion would make it more statistically significant.

(4) Relation of Incidence of Heart Damage in ACTH- and Cortisone-treated Rheumatic Fever to Dosage and to Duration of Illness. By SUJOY B. ROY and BENEDICT F. MASSELL, *Boston, Mass.* (By invitation.)

Of 140 rheumatic fever patients (under 17 years of age) in initial attacks, 56 (Group A) were treated for 6 weeks with a total of 4·1 g. cortisone or 1,100-2,500 units ACTH, and 84 (Group B) were treated for 12-16 weeks with a total of 13-15 g. cortisone or 4,100-7,000 units ACTH. Group A included the patients contributed by the House of the Good Samaritan to the Cooperative Rheumatic Fever Study.

On discharge from the hospital, heart damage was present in 70 per cent. of Group A (small dose) and 38 per cent. of Group B (large dose). Incidence of heart damage was also related to the duration of illness. Thus, for duration sub-groups the incidence of heart damage was as follows:

Days	Group	
	A	B
0– 7	30	19
8–14	69	24
15–42	80	45
Over 42	100	79

The frequency with which significant murmurs, present at the beginning of therapy, disappeared was 20 per cent. in Group A, and 40 per cent. in Group B. This incidence was also related to the duration of illness. Thus the incidence of disappearance of significant murmurs was as follows:

Days	Group	
	A	B
0– 7	50	62
8–14	25	43
15–42	13	40
Over 42	0	17

Groups A and B with significant murmurs at start of therapy were comparable regarding such important manifestations as cardiac enlargement, pericarditis, congestive failure, and subcutaneous nodules.

The data, though not conclusive, strongly suggest that good results of hormone therapy are dependent on prompt treatment with relatively large doses, given over a relatively long period.

Discussion.—DR. DENNISON YOUNG (*New York City*): This problem bothers us all constantly. Dr. Roy and Dr. Massell have had considerable experience for many years with this disease. What can they tell us about the incidence of carditis in a comparable group of patients treated within the last 2 years with bed rest alone?

DR. EDWARD E. FISCHEL (*New York City*): It seems almost axiomatic that any disease will do better the earlier we treat it. I think this very point "discoloured" the therapy of rheumatic fever with salicylate for many years; people failed to consider that groups with and without therapy of any kind should be compared with similar groups as regards duration of active disease before the observation period.

In the Cooperative Study the duration of illness before therapy was a significant factor in the outcome, perhaps more so than the kind of drug used.

I do not like to be characterized as a member of the pessimistic group that felt that the hormones were, at the most, no better than aspirin. We were optimistic enough to think that both drugs do good if given early, in large dosages, and for a fairly long time.

DR. ROY: In reply to the first question of Dr. Young, we have not yet got all the data ready, but we have enough evidence to state that before the introduction of hormone therapy, young children admitted with acute congestive failure used to die like flies.

I feel honoured that Dr. Fischel has spoken, for I thought his paper on long-term salicylate administration* was very good. I come from a poor country where we had to use salicylate, unless some foreign firms gave us free hormones.

His statement is complementary to what we have said, we did not mean to suggest that aspirin is a better drug than the hormones or not. We were just trying to submit, very humbly, that divergent opinions on this subject may in part be due to not taking the duration of the illness and the size of the dose into consideration. I know that a very famous lady sitting here believes you do not have to give it for a long time, and that 7 days is probably long enough. We haven't tried it, but she finds wonderful results, and I see no reason why others should not do the same.

DR. MAY G. WILSON (*New York City*): I am very happy that it has finally been impressed upon a great many people that it is important to treat early, and important to treat with a large enough dose. I hope by next year to hear that you do not have to give it so long.

(5) Effect of Intensive and Prolonged Cortisone and Hydrocortisone Therapy in First Attacks of Rheumatic Carditis. By MILTON MARKOWITZ, *Baltimore, Md.*, and ANN KUTTNER, *New York City*. (By invitation.)

Cortisone is an effective agent for the suppression of the inflammatory reaction caused by rheumatic fever, but whether cardiac damage is prevented or diminished by the suppression of inflammations is not known. Greenman and his co-workers reported a low incidence of residual heart disease in patients developing carditis during their first rheumatic attack treated early with large daily doses of oral cortisone. In view of these findings, further studies of the effect of large doses of cortisone or hydrocortisone were undertaken.

Forty patients with first attacks of rheumatic fever with clinical evidence of carditis were treated. All received either 200 or 300 mg. oral cortisone or oral hydrocortisone daily for 6 weeks. In eighteen of these patients, the

* Fischel, E. E. (1952). *Medicine (Baltimore)*, **31**, 331.

dosage was then tapered over a 3-week period. In the remaining 22, after 9 weeks of therapy, a maintenance dose of 50 mg. cortisone daily was continued for 2 to 10 months. Patients with exacerbations of carditis after the termination of therapy were re-treated with 50 mg. cortisone daily for 4 to 8 weeks.

Of these forty patients, 29 received treatment within 3 weeks or less of onset. After follow-up observations ranging from 6 to 22 months, 24 of these 29 patients have no evidence of heart disease. Patients with severe as well as mild carditis responded equally well.

Eleven patients treated later than 3 weeks after onset did less well. Only two have normal hearts; eight have rheumatic heart disease and one has died.

Apart from minor signs of the Cushing syndrome, eleven of the forty developed undesirable side-effects.

The results suggest that cortisone, given early in the course of the rheumatic attack in large doses and continued until the disease has run its course, may reduce the incidence of residual heart disease.

Discussion.—DR. HARRY A. FELDMAN (*Syracuse, N. Y.*): I believe we are witnessing something of the completion of a cycle. Several years ago we heard a great deal of discussion about the reversibility of the acute rheumatic lesion or the reversibility of rheumatoid arthritis as a result of steroid therapy.

Given treatment at a certain (but as yet undefined) stage of active rheumatic fever, one cannot expect *total* reversion to a normal tissue state, but, given adequate treatment at the proper time, one may expect substantial reversion to the pre-attack state in many patients.

The question should be, what is "adequate" dosage? It makes no difference whether the dose is "large" or "small". We have to administer a certain amount of a given drug in order to obtain an optimal therapeutic response, and we should know what those amounts are; I think we should speak in terms of "adequate" rather than of "high" or "low" doses.

The patients who died during therapy are of special interest; if one examines such cases as reported in the literature, it seems that most of these seem to be patients who were started on steroid therapy rather late in the course of their acute rheumatic fever. I don't quite understand this, and it would be of interest for some of us to keep watch on this to determine whether this is more than just an impression.

In our own hospital we have recently had such a death. Treatment was started in the sixth week of the illness and the patient died some 5 or 6 days later. There may have been no causal relationship, but I believe that I have encountered three such cases in the literature, and there was also one in the paper just presented by Dr. Markowitz.

Having said that, I shall proceed to discuss our own experiences (in conjunction with Dr. Leo Jivoff) with prednisone* in the treatment of acute rheumatic fever. We have treated ten such patients in recent months, each of whom had active carditis; six were children and four were adults. Our dosage schedule was set up like this:

First day 50 mg. in four 6-hrly doses.
Second day, dose reduced to 40 mg.
At 96-hr intervals, depending upon maintenance of clinical improvement, dose decreased by 5 mg. daily.

* Supplied by the Schering Corporation.

We found that the usual symptomatic response was rather good with this dosage schedule. The temperature dropped to normal within hours, and joint pain was relieved rather quickly, but signs of joint effusion lingered in most patients for 4 to 5 days. The C-reactive protein reverted to normal usually in 7 days with the erythrocyte sedimentation rate somewhat more slowly.

The anaemia, when present, corrected itself rather promptly, so that by the 8th to 10th day, there was usually a very noticeable improvement in both the haemoglobin and haematocrit. None of these patients was on a sodium-restricted diet and there was no evidence of abnormal water-retention.

Because five of these patients required re-treatment on this schedule, it appeared to us that we might not be giving sufficient medication. When another patient came in with severe carditis, we decided to increase the dose to 100 mg. initially and then drop to 90 mg.—in other words, to double the previous schedule. On the 6th day of therapy this patient developed frank congestive failure, and withdrawal of the drug led to diuresis and clearing of the failure. The carditis did not seem to be benefited, but it had been present for some weeks. This experience suggests that in doses such as these sodium had better be restricted, even with prednisone.

Five patients developed mooning of the face and in three acne appeared in 10 to 14 days.

One patient died (whom I mentioned earlier) and at autopsy was found to have active pancarditis. She also had chorea and some bronchial pneumonia.

One patient developed staphylococcal pneumonia which went on to abscess formation but resolved satisfactorily when the steroid was withdrawn and antimicrobial and salicylate therapy instituted.

In ten patients, then, with acute rheumatic carditis on the dosage schedule described, the response was generally good; I think that prednisone deserves considerably more study, but as yet we have no notion of what constitutes adequate dosage.

DR. JOSEPH J. BUNIM (*Bethesda, Md.*): These two papers, by Drs Roy and Massell and by Drs Markowitz and Kuttner, are of extraordinary importance. Their observations can readily be reconciled with evidence obtained experimentally. From tissue culture and the animal studies reported by Leon Weiss, it becomes evident that there is a phase in the development of the inflammatory process at which the mononuclear cell, derived from either the circulating blood or connective tissue, becomes transformed into a macrophage. As this transformation occurs, the macrophage acquires both adaptive and constitutive enzymes. Moreover, monocytes may then fuse into multinucleated giant cells.

It is therefore conceivable that when an anti-inflammatory agent, such as cortisone, hydrocortisone or prednisone, is administered, it may, if given early enough, cause a recession of the inflammatory process at such a strategic time as might inhibit the transformation of the mild-mannered monocyte to the more aggressive and predatory macrophage.

Let us add to this observation the results reported by Thomas Dougherty, who induced inflammation in the subcutaneous tissue of mice by injecting standard doses of phlogistic substances, such as histamine-diphosphate, pyrogen or gelatin, and 6 hours later counted the inflammatory cells totally and differentially. This affords a reliable means of measuring the degree of inflammatory response and correspondingly the anti-phlogistic potency of various anti-inflammatory agents. Dougherty found

that cortisone and, to a much greater degree hydrocortisone, possessed anti-phlogistic properties. It should be emphasized that he also established a correlation between the size of the dose and the anti-inflammatory effect of the steroid. Thus it becomes evident from experimental observations that time and dose are both extremely important factors.

In closing, I should like to add that in a joint study with Dr. Markowitz and Dr. Charlotte Ferencz of Johns Hopkins University, we have studied the clinical and metabolic effects of large doses of prednisone in thirteen children treated during the first 26 days of initial attacks of acute rheumatic carditis. Thus far, nine have been treated for at least 5 weeks. Unequivocal organic murmurs present before therapy have already disappeared in seven of the nine patients, and these seven children now have no signs of organic heart disease. All but one of the patients in the series are still receiving prednisone, which we plan to give for no less than 14 successive weeks. None of the patients developed oedema, sodium retention, hypokalaemia or congestive heart failure, yet all were on unrestricted sodium.

DR. CURRIER MCEWEN (*New York City*): I am glad that Dr. Feldman made the comment he did that one should use "adequate" suppressive dosage and not think of dosage in terms of "small" or "large". It seems to me that it should be possible as time goes on to adopt as the guiding principle, not a given size of dose for a certain number of weeks until the attainment of certain effects, such as the disappearance of gallop, heart failure, tachycardia, and laboratory evidence of inflammation, and to use doses large enough to achieve these effects as required by the individual patients.

I think we may probably accept to-day that if a patient is treated early with a drug that is capable of suppressing rheumatic inflammation, the results are hopeful; in that sense we are far better off than we were 5 or 10 years ago, when we felt that none of our suppressive drugs really had much effect on the carditis.

The question whether cortisone or other steroids are superior to salicylates in that suppressive action remains unsettled. I think most of us would consider the steroids more potent in antirheumatic suppressive power than the salicylates, but I suspect most of us would agree to-day that the difference is probably merely one of degree. Finally, in connexion with Dr. Fischel's remark about the good effects obtainable with salicylates, we should not forget this tried and true agent, and I should like again to support the view that salicylates and steroids may advantageously be used together.

DR. MORRIS ZIFF (*New York City*): My question concerns the time interval before one institutes cortisone. Does a waiting period eliminate some of the mild cases so that one obtains poorer results with the remaining group? Could this explain the less favourable results the longer one waits to start therapy?

DR. MARKOWITZ: I think that is an important point. I think Dr. Ziff knows the answer to it, because some of these patients were from his group. We should like very much to wait 24 to 48 hours; despite the fact that we advise early therapy, we do not like using this involved and even risky treatment unnecessarily. So that waiting 24 to 48 hours in such a patient and making certain of carditis and, indeed, of the degree of carditis, would seem to me to be very much in order.

It has been the custom in some places to give aspirin for 24 to 48 hours and so reduce the fever; often a striking reduction in tachycardia and a striking improvement in heart sounds indicates that carditis is absent and hormone therapy not indicated. We feel very strongly, at present, that hormone treatment should be limited to patients with very clear-cut carditis.

DR. ROY: In Boston we are carrying out a study which is comparable with the Cooperative Study except that we are dealing with a larger amount of cortisone or ACTH, and that the criteria are exactly those of the Cooperative Study. We are really not waiting, but trying to catch cases as early as possible. So far, we have been very lucky in that we have not many side-effects. We lost one patient with chicken-pox.

Dr. McEwen's suggestion that we use the term "adequate suppressive dosage", is very good. We showed "small" doses and "large" doses to illustrate our point; what we really are talking about is an "adequate" dose.

We believe aspirin has a suppressive effect, and the answer will come when we get enough cases to analyse. We have only about ninety cases so far, but we expect another hundred in the next year, and then maybe we shall be able to say more about it.

* * * *

Course of Severe Rheumatoid Arthritis during Four Years of Induced Hyperadrenalism. By DAVID S. HOWELL, *New York, N.Y.* (Introduced by Dr. Charles Ragan.)

68 patients with rheumatoid arthritis have received cortisone, ACTH or hydrocortisone during a period of 6 months to 5½ years. The duration of disease was 3 years or longer in 90 per cent. of the series and 61 patients exhibited advanced arthritic lesions by *x* ray (Stages 3 and 4 by the Steinbrocker classification). The dosage of cortisone and ACTH was held throughout the study at levels which produced suboptimal relief of symptoms in order to reduce complications. The hyperadrenal state was terminated in five patients because of a remission and in 27 patients because of untoward events. In the latter group were eleven deaths, and follow-up of twelve of the rest 2 to 3 years after discontinuation of hyperadrenalism revealed that eleven remained confined to a bed or chair. At the close of the study 36 patients remained on cortisone or ACTH. This group continued to manifest physical signs and laboratory evidences of rheumatoid activity, and in 21, progressive destruction of joints during hyperadrenal therapy was demonstrated by serial *x* rays. Attempts to terminate hyperadrenal treatment in this group have not been successful because of prompt rebounds, but ACTH and cortisone have continued to produce moderate or marked symptomatic relief in the majority.

Discussion.—DR. JOSEPH J. BUNIM (*Bethesda, Md.*): It is clear that patients who have mild rheumatoid arthritis and have done well on conservative measures should not be given steroid therapy, but how about those who have very severe rheumatoid arthritis? When a patient's disease is progressing rapidly and seems to show no signs of tapering off, that, in itself, seems to me the best indication for the institution of steroid therapy.

DR. HOWELL: In general, we agree on this point, but our experience suggests that if those patients who are progressing rapidly have associated inflammatory disease such as chronic pyelonephritis or bronchiectasis, the chance of salvaging them is very poor.

DR. EDWARD F. HARTUNG (*New York City*): Was the presence of amyloid degeneration determined in these chronic, well-established cases that did poorly, and is amyloid degeneration a factor in the poor results and the deaths?

DR. HOWELL: Two patients showed amyloidosis at autopsy which may well have contributed to their downhill course; in one of them amyloidosis was diagnosed several years before death.

DR. JEROME SIMSON (*Forest Hills, N.Y.*): How was the *x*-ray improvement manifested?

DR. HOWELL: Three of the five showed *x*-ray improvement; in two of these, it was merely a reduction of osteoporosis, in the third there was actual healing of punched-out bone lesions.

Heart in Rheumatoid Arthritis: A Clinical-Pathologic Correlation of 43 Autopsied Patients. By M. H. LEVIN, L. KAPLAN, S. MARCUS, H. J. WEINBERGER, and J. PATTERSON, JR., *Los Angeles, Calif.*

In an attempt to establish the clinical and pathological cardiac manifestations of rheumatoid arthritis, 43 autopsied cases were studied. The pathological findings were as follows:

Granulomatous lesions resembling subcutaneous rheumatoid nodules	10
Obliterative lesions of the pericardium	12
Nodular thickening of one or more valves	25
Inflammatory lesions of the ascending aorta	7
Amyloid infiltration	7
Arteritis of the coronary vessels	7
Arteriosclerotic heart disease	15
Cor pulmonale	7
Non-specific myocarditis	2
Granulomatous pericarditis	2

The pathological changes were correlated: age, sex, duration and classification of arthritis, presence of subcutaneous rheumatoid nodules, steroid therapy, psoriasis, iritis, clinical cardiac findings, congestive heart failure, response to therapy for congestive failure, electrocardiographic alterations, cardiac roentgenograms, other major diagnoses, and cause of death.

Clinically, arteriosclerotic heart disease was not distinguishable from the inflammatory alterations encountered in the hearts of these patients with rheumatoid arthritis, with the sole exception that in the presence of congestive heart failure the response to therapy of the two groups was usually good and usually poor respectively. Nonetheless, these data further substantiate the concept of rheumatoid heart disease as a multiphasic entity with many pathological manifestations. The observations seem to indicate that a given patient with rheumatoid arthritis, even an older individual, has a greater likelihood of having rheumatoid heart disease than arteriosclerotic heart disease.

Discussion.—DR. WILLIAM S. CLARK (*Cleveland, Ohio*): Dr. Levin has provided more evidence that there is a rheumatoid form of heart disease. Data so far accumulated indicate that three types of inflammatory lesions occur in the heart in rheumatoid arthritis:

(*a*) unquestionably rheumatic in nature,
(*b*) seeming to be rheumatoid in origin,
(*c*) unclassified.

I think we are reasonably sure that the nodule represents a form of rheumatoid heart disease, as does the aortitis which Dr. Levin demonstrated.

He observed a high incidence of nodules in these hearts, but it seemed to me that about half of his patients were nodule formers, and that may explain the higher incidence in this series of cases.

DR. EDWARD F. ROSENBERG (*Chicago, Ill.*): It certainly has been interesting to watch developments in the past 14 or 15 years since Dr. Vogenoff and I presented a paper here before this society; papers from different parts of the world report quite different findings in this matter of the heart in rheumatoid arthritis.

It is reported by Egelius, Göhle, Jonsson, and Walgren* from Stockholm that they found little or nothing excepting perhaps a little pericarditis in an autopsy series. They concluded that there must be something wrong with the work that others, including Dr. Vogenoff and I, had done in finding these rather extensive cardiac lesions.

The subject does not seem to be settled even to-day, although the paper we have just heard supports those who find rheumatoid arthritis to be associated with cardiac damage.

In the past it was of academic interest to find that there were lesions in the heart, because clinicians said that as rheumatoid arthritis patients do not have much heart trouble we should just take note of it and not worry too much about it. But in the future, this may not be the case. For example, difficulties are resulting from the discovery of a remedy which frees the movements of rheumatoid arthritics, because osteoporosis leads to fractures; these cardiac lesions may also become more important as bedridden patients are able to get up.

Were any of these autopsied patients observed in recent years after having hormone treatment, and did it make any difference?

DR. LEVIN: These patients were autopsied consecutively from 1947 to the present time, and I have four additional cases which were autopsied very recently. Every patient with rheumatoid arthritis who has died in our institution has come to autopsy.

The data on the administration of steroid therapy was interesting. Approximately ten of these patients were on steroids and in several we found changes of the variety described. When the incidence of the various types of changes encountered in the group who received steroids was correlated statistically with the remainder of the group, no significant difference was noted.

DR. CURRIER MCEWEN (*New York City*): Since lupus raises its ugly head in so many of these diseases, was it explored in these particular patients?

DR. LEVIN: Diagnostic lupus cell preparations were not done in most of them, but no evidence of lupus was seen in the kidneys.

DR. DONALD GRAHAM (*Toronto, Ont.*): Did Dr. Levin find any lesions in the ascending aorta in patients who did not have spondylitis?

DR. LEVIN: Yes. Of the eight patients with aortitis, four had had peripheral arthritis only. Of the other

* *Annals of the Rheumatic Diseases* (1955), **14**, 11.

four cases, three had combined peripheral and spinal arthritis, and one had pure spondylitis.

DR. JOSEPH J. BUNIM (*Bethesda, Md.*): Of the 43 patients who were autopsied, 25 showed a nodular valvulitis in one or more valves; and 27 showed clinical evidence of cardiac abnormalities. I wonder what the physical examination of the patients now living in the same hospital would reveal.

In this particular group the sex ratio was much higher than in any ordinary group, since 97 per cent. were males, and that might account for some of the difference.

DR. LEVIN: We are aware of the difficulty in drawing conclusions from data on autopsied series. Dr. Mainland's work, pointing out the dangers encountered in trying to draw conclusions on the basis of autopsied material, is well known to us.

We do know our data are weighted because these patients were all veterans; they were primarily males with severely advanced rheumatoid disease, they had all been in the institution for a long time, and they all died. There are also probably other unknown factors.

We find a much lower incidence of detectable heart disease in living patients with rheumatoid arthritis, and this parallels the clinical findings described in recent publications, about 15 to 20 per cent.

DR. H. A. SMYTHE (*Toronto, Ont.*): I wonder if any important differences were noted between rheumatoid arthritis and spondylitis with regard to the heart lesions. In the large clinical series in Sunnybrook Veterans Hospital at Toronto, there are two important differences between the two groups: In the spondylitics there is a much higher incidence of lone aortic regurgitation, and a much higher incidence of long PR intervals or second degree heart block.

DR. LEVIN: We analysed the data from that point of view and found no difference between people with spondylitis and those with peripheral involvement. As far as the electrocardiograms were concerned, we found all kinds of varieties of E.C.G. abnormalities. Heart block was more common in the small number of patients who had uncomplicated arteriosclerotic heart disease than in those with rheumatoid heart lesions.

Nodular Vasculitis: A Manifestation of Systemic Rheumatic Disease. By PAUL J. VIGNOS, JR., J. LOWELL ORBISON, and WILLIAM S. CLARK, *Cleveland, Ohio.*

Nodular vasculitis has been described by Montgomery and others (1945)* as a localized skin disease characterized by chronic nodular lesions of the lower legs. Three patients will be discussed in whom the local nodular vascular lesions were associated with systemic involvement, suggesting that they may be manifestations of generalized rheumatic disease.

The nodose lesions occurring on the lower legs, for periods of 3 to 16 years, were painful, chronic, recurrent, and non-ulcerative. Systemic manifestations in all three included non-deforming, chronic arthritis which was a major complaint and antedated the nodules. Other systemic manifestations were myositis, hypertension, episcleritis, migraine headaches, and abdominal haemorrhage. Differential sheep cell agglutination tests were negative. "L.E." cells were present in one.

Histopathological studies of the skin revealed inflammation and necrosis of arteries and veins deep in the dermis and in the subcutaneous fat. All patients had lesions characterized by necrosis of the vessel walls accompanied by acute inflammation. In addition to this acute lesion, two patients had scarred and distorted vascular walls and a large lumen filled with connective tissue; these sites of previous injury were unusual in that recent coagulative necrosis had been superimposed on the old injury and had partially destroyed the connective tissue in the lumen and also the vessel wall. Apparently the lesions not only tend to recur, but to recur at sites of previous lesions.

Discussion.—DR. THEODORE B. BAYLES (*Boston, Mass.*): With Dr. Edward Edwards at the Peter Bent Brigham Hospital and Robert Breck Brigham Hospital, we have been interested in these vascular lesions for the last 2 or 3 years. Am I right in thinking that the patients described had classical rheumatoid arthritis?

We have observed haemorrhage into the subcutaneous tissue, and I should like to know whether this was observed by you? We think that this primarily involves the vein, although you mentioned arterial involvement.

Our patients mostly had this lesion on the dorsum of the foot, and I wonder where the lesions were located in your patients.

DR. VIGNOS: The arthritis exhibited by our patients was not typically rheumatoid in nature. Joint complaints had been present for many years with episodes of synovitis in all, but none had deforming arthritis.

We have seen no skin haemorrhages, nor other lesions of the haemorrhagic or necrotic type such as are frequently seen in lupus erythematosus or periarteritis nodosa. There were no skin lesions except the nodules, and we feel that this was an unusual feature in view of the high incidence of varied skin lesions in lupus erythematosus and periarteritis. There was involvement of both arteries and veins in these patients.

These lesions frequently appeared on the anterior aspect of the lower leg at the pre-tibial level. They appeared posteriorly in the soft tissue overlying the gastrocnemius muscle, and also in the ankle region, near the malleoli. We have seen only a few lesions over the dorsum of the foot, which was one of the less frequently involved sites.

DR. J. P. HAMILTON (*Memphis, Tenn.*): Was there a history of allergy in any of these patients?

DR. VIGNOS: We did not elicit a history of allergy in any of them; there has been no asthma nor other manifestation that might be listed under that heading.

Behaviour of the Agglutination Activating Factor of Rheumatoid Arthritis with Immune Precipitates. By JOHN H. VAUGHAN, *Richmond, Va.*

The agglutination activating factor (AAF) of the sera of individuals with rheumatoid arthritis (Rose, Ragan, Pearce, and Lipman, 1948) is capable of interacting with several types of cells sensitized with antibody of various animal species (Pike, Sulkin, and Coggeshall, 1949; Wager, 1950). This apparent lack of immunological specificity of AAF has suggested that its behaviour may be more like that of serum complement than that of serum antibody and that it might be profitably studied with immune precipitates.

* *J. Amer. med. Ass.* (1945), **128**, 335.

Washed immune precipitates from antisera of rabbits immunized with recrystallized egg albumin (Ea) or conalbumin (Ca) were added to heat-inactivated rheumatoid and normal human sera. Increasing quantities of Ea-anti Ea absorbed increasing amounts of nitrogen from the rheumatoid arthritis sera. No nitrogen was absorbed from individual or pooled normal sera. With the absorption of increasing quantities of nitrogen from the rheumatoid arthritis sera, the AAF activity of the supernatant was first reduced and then abolished completely. In control studies, powdered asbestos, filter paper, and barium sulphate did not absorb any measurable nitrogen nor reduce the AAF titre. Ca-anti Ca precipitates behaved similarly to Ea-anti Ea precipitates.

The interaction of AAF with immune precipitates appeared to be an equilibrium reaction. Whereas a plateau of absorbed nitrogen was reached by the addition of increasing quantities of Ea-anti Ea to given volumes of rheumatoid arthritis sera, new Ea-anti Ea added to the supernatants at the plateau level absorbed some additional nitrogen. The total amount of nitrogen absorbable from high-titre rheumatoid arthritis sera was 100-200 μg. N/ml., a value corresponding to about 1-2 per cent. of the total protein of the sera.

The use of immune precipitates for the study of AAF offers a promising tool for the further development of our understanding of the nature of this factor.

Discussion.—DR. MORRIS ZIFF (*New York City*): Dr. Vaughan's work seems to me to be of great importance. For the first time the sensitized sheep cell agglutination reaction, which has hitherto been based on an indicator system which could not possibly play a role in human disease, has now been related by Dr. Vaughan to the type of immune system which might play a role.

DR. RALPH H. BOOTS (*New York City*): Despite the many reports yesterday of investigations of adrenal cortical hormones, it is still highly questionable whether the secrets of rheumatoid arthritis will be answered by this approach, and it is refreshing to have a paper such as Dr. Vaughan has given this morning which has nothing to do with steroid hormones.

The younger research workers in this society should be encouraged to try other types of attack on this disease and I wish to congratulate Dr. Vaughan on continuing his work with the immunological approach.

Natural History of Marie-Strümpell Arthritis (Rheumatoid Spondylitis). By BARUCH S. BLUMBERG, *New York, N.Y.*

During the past 28 years, the diagnosis of Marie-Strumpell arthritis, or rheumatoid spondylitis, has been made on approximately 300 patients at the Presbyterian Hospital. We have been able to contact more than 50 per cent. of these patients and personally interview, examine, and perform blood tests and *x* rays on over one hundred of them.

There is a follow-up of 20 years or more in many of these patients and in most cases, *x*-ray and laboratory confirmation of the clinical findings are available. On the basis of these data, we have reached some conclusions concerning the natural history of this disease.

The material has been co-ordinated by plotting certain objective and subjective data as a function of the duration of the disease. This suggests that, in the typical case, the progression of the objective *x*-ray findings is relentless, while the functional disability and pain are by no means so, and may, indeed, appear to improve. The data also suggest that there is a period of rapid progression of *x*-ray and physical findings early in the disease. These objective changes then reach a plateau at which the patient appears to adjust and then to carry on his activity with remarkably little functional disability. The final bony involvement is variable and only a few go on to marked deformity. This should be appreciated in evaluating the necessity for radical therapy in the early stages of the disease.

Many of the patients have had symptoms of peripheral arthritis, but only a few subsequently developed objective changes in the peripheral joints. It is the latter group which seems to do less well.

Persons with rheumatoid spondylitis appear to be very effective. They are for the most part married and have children. They are nearly all working and maintaining themselves even in the face of apparently overwhelming skeletal deformity.

Discussion.—DR. IVAN F. DUFF (*Ann Arbor, Mich.*): The details of the extent of involvement of the spine or sacro-iliac joints at the time of initial examination is of particular interest to us. In 1940 Dr. Charlie Smyth and Dr. Richard Freyberg reported to this group the effect of *x*-ray therapy on selected patients with rheumatoid spondylitis. Dr. W. D. Robinson made a second report in 1947. A third follow-up study was conducted by the Rackham Arthritis Research Unit, with particular reference to the effect of *x*-ray therapy in fifty patients who at the initial examination, 7 to 16 years ago, had no *x*-ray evidence of involvement of the sacro-iliac joints (5), changes limited only to the sacro-iliac area (31), or changes limited to the sacro-iliac joints and lumbar spine (14). This work was made possible by the efforts of Dr. Keith Averill who carried it out while holding a vacation fellowship as a senior medical student.

In our series there was no control group of patients with spondylitis not treated with *x*-ray therapy. For this reason we have listened closely as Dr. Blumberg has described the natural history of the disease. It is of interest that our experience is quite similar to that reported by him. In this group 82 per cent. did well symptomatically, and 60 per cent. pursued a favourable objective course, but in approximately 40 per cent. there was relentless progression of the disease as demonstrated by the *x*-ray changes throughout the spine and neck.

In our experience there appears to be some relation between the benefit of *x*-ray therapy and the duration of the disease. Those who had had spondylitis for less than 2 years did better symptomatically and objectively than those who had had it for a longer period. This point is of significance perhaps in relation to early diagnosis.

Peripheral joint involvement, which in our experience may antedate the back symptoms, occurred at some time in almost 50 per cent. At the end of our study, however, objective manifestation of active peripheral involvement was not frequent. Indeed, only one patient at the last follow-up was taking steroids to control symptoms related to peripheral involvement. Peripheral joint involvement in spondylitis does not necessarily behave as one might expect from one's experience of

rheumatoid arthritis without spondylitis. In spondylitis it is apt to pursue an indolent course, and some of the patients who become free of back complaints do very well despite obviously swollen joints. In a few patients with active involvement in the back, improvement in the peripheral synovitis, particularly of the knees, appeared coincident with improvement related to *x*-ray therapy.

In our group, girdle-joint involvement appears to have developed late in the course of the disease. Manifestations of girdle-joint involvement developed in at least 50 per cent.; in approximately 16 per cent. hip involvement had become a major disabling problem. Eye disease was also important, since iritis or similar involvement was observed at some time in fourteen of the fifty.

We agree with Dr. Blumberg that, by and large, as representatives of the rheumatic diseases, the patients with rheumatoid spondylitis often appear to be superior individuals. They frequently make a good adjustment to their disease and its limitations, and are productive citizens in spite of it. This is not to deny, however, that spondylitis, particularly when accompanied by bizarre skeletal deformity, as of the cervical spine, or by blindness, can be a frightful disease.

DR. BLUMBERG: All the patients we evaluated had involvement of the sacro-iliac confirmed by *x* ray. This group was perhaps somewhat more severely involved than one would find in a private practice.

Some of our patients had received *x*-ray therapy and some not, but the two groups were not randomly selected and are therefore not comparable, though we found that those who did not receive radiotherapy had somewhat more physical deformity than those who did.

DR. CORNELIUS H. TRAEGER (*New York City*): In this remarkable group of patients and wonderful follow-up which Dr. Blumberg had, there are two aspects which were not commented on and I wonder if Dr. Blumberg had made these observations. First, in the large majority of patients who were able to continue work, was it ever necessary for them to change their occupation during the development of the disease?

And secondly, were there any familial tendencies or hereditary factors observed in this group?

DR. BLUMBERG: Some of them did change their occupation, but most of them work for remarkably long times at responsible and physically difficult jobs. We had one woman who, after having been seen in our hospital, went home and spent the next 10 or 15 years picking cotton. I think, as a rule, they maintain their jobs fairly well, although we did not study the occupational history in great detail. We were satisfied to determine their gross functional status.

There was a definite familial incidence. We had two families in which there were more than two members involved, in one case two brothers and a sister, and in a second the patient, his father, grandfather, and great grandfather.

DR. PAUL H. CURTISS (*Cleveland, Ohio*): Was any note taken of any surgical procedures such as orthoplasty, and did it have any effect on change in classification or course?

DR. BLUMBERG: There were two patients who had osteotomies of the spine in this group and they were doing well, with a good cosmetic result. However, it is difficult to determine whether they would have done well had they not had the operation, as many of those who were not treated surgically also did well.

DR. JOHN G. KUHNS (*Boston, Mass.*): I dislike injecting a pessimistic note into this very interesting study. We followed some four hundred cases of spondylitis for from 5 to 14 years and our functional results are inferior to those Dr. Blumberg has mentioned; 35 per cent. had ankylosis of the hips, 30 per cent. had peripheral joint involvement, at least 10 per cent. had iritis with blindness or some damage to the eyes before the advent of hormone therapy, and at least 20 per cent. had operations for various gastric difficulties.

DR. BLUMBERG: What was their functional ability?

DR. KUHNS: Only about 50 per cent. of them could be considered in Group I.

DR. BLUMBERG: A good number of our patients had peripheral joint involvement, but a digression might be made on this point. Some 60 per cent. of the patients gave a history of peripheral joint involvement. However, only half of that number, about 30 per cent. of the total, actually showed objective changes of joint involvement when we saw them.

Of those who had the peripheral joint involvement, it was practically all in the hips and knees and perhaps to a somewhat lesser extent the shoulders. The involvement of the wrist and fingers, so characteristic of typical peripheral rheumatoid arthritis, was extremely rare in the group that we saw. There were only four or five out of perhaps one hundred who had evidence of objective wrist and finger involvement.

The difference in selection of the groups, among other things, could account for our different results.

Pathways of Urate Synthesis in Gout. By JAMES B. WYNGAARDEN and ALBERTA BLAIR,* *Bethesda, Md.* (introduced by J. J. Bunim). Read by Dr. S. Segal.

The present study was designed to compare rates and extents of glycine incorporation into purines of normal and gouty persons, to gain information about the biosynthetic intermediates of normal and abnormal urate production. One control (osteo-arthritic) and two gouty men were given 5 μc. glycine-1-C^{14} (0·13 mg.) orally while on a purine-free, low-protein diet. Urinary purines were isolated as copper salts and dissolved in HCl, and uric acid separated by reduction of volume and chilling. Residual purines were further purified *via* copper and ammoniacal silver precipitations, and placed on Dowex-50-H^+ column (200-400 M, 2·5 × 12 cm. bed) as hydrochlorides. Separation was achieved by gradient elution with HCl (0·15→2·65 N). Purines were recovered, recrystallized, and counted.

In the control, urate specific activity reached a maximum of 350 c.p.m./mM on the third day. Hypoxanthine specific activity was greater than urate on Day 1, and fell rapidly to low values by Day 3. Adenine values, however, were maximal on Day 3, and declined in parallel with urate, but at values approximately half those of urate. Xanthine values were about 90 c.p.m./mM throughout the study, suggesting appreciable dilution of labelled xanthine by xanthine derived from metabolically less active sites. The hypoxanthine data suggest a rapid pathway for urate synthesis in the normal, possibly *via* inosinic acid; the adenine data suggest a second slower

* National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U.S. Department of Health, Education, and Welfare, Bethesda, Md.

pathway, quantitatively the more important, possibly involving nucleic acids. One gouty subject who excreted normal quantities of urate showed a strikingly abnormal pattern of glycine incorporation. Urate specific activity was 910 c.p.m./mM on Day 1, followed by a precipitous decline. A second gouty subject who excreted excessive quantities of urate (1,135 mg./day) also showed an exaggerated rate and extent of glycine incorporation into urate. In this subject hypoxanthine enrichment was maximal on Day 1 and thereafter declined slowly. Hypoxanthine values were at all times less than those of urate. These results suggested that the "inosinic acid pathway" was involved in both rapid and excessive urate synthesis in this subject, but also suggested the possibility of an accessory pathway for urate synthesis, not involving the usual intermediates, responsible for a part of the over incorporation of glycine into urate.

Clinical Course of Acute Gouty Arthritis treated with Oral Phenylbutazone: Relationship of Drug Dosage Schedule and Serum Drug Level. By GEORGE M. WILSON, JR., ELSTON R. HUFFMAN, and CHARLEY J. SMYTH, *Denver, Col.*

The control of the manifestations of acute gouty arthritis by phenylbutazone has now been well established. However, the characteristic pattern of the response of gout to the drug, and the rapidity of response as related to the drug dosage schedule and effective serum levels, have not been sufficiently emphasized.

Sixty consecutive attacks of acute gouty arthritis, occurring in 42 males, were treated with various dosage schedules of oral phenylbutazone. A similar pattern of response to the drug was observed in all cases. This was characterized by two phases. Initially, a marked subjective (50-100 per cent.) relief of joint pain occurred without significant objective changes in the other signs of joint inflammation. 24 hours or more later, complete resolution of all evidences of joint inflammation occurred. In 56 attacks (89 per cent.), subjective pain relief occurred within 24 hours. In 49 attacks (73 per cent.) complete resolution of all findings of inflammation occurred within 72 hours.

The promptness with which the two phases of the response occur, varied with the dosage schedule of phenylbutazone. When a 400 or 800 mg. stat dose was given, relief of pain occurred within 4 hours in 16 of 19 attacks occurring in 19 patients. Complete resolution within 24 hours occurred in 8, and within 24 to 72 hours in 15. When 100 mg. every 4 hours (400 mg./day) was given, pain relief occurred within 4 hours in only two of 22 attacks occurring in sixteen patients; sixteen attacks were relieved in from 4 to 12 hours. Complete resolution within 24 hours occurred in fourteen attacks, and in from 24 to 72 hours in seven. When 200 mg. every 4 hours (800 to 1,200 mg./day) was given, pain relief occurred within 4 hours in only one of fifteen attacks in eight patients. Thirteen attacks were relieved in from 4 to 12 hours after drug ingestion. Resolution within 24 hours occurred in six attacks, and in from 24 to 72 hours in seven.

These observations indicate that the pain of acute gout is most promptly relieved by a 400 or 800 mg. stat dose of phenylbutazone. Complete resolution of the attack occurs earliest with an intermittent dosage schedule. It is recommended, therefore, that acute gout be treated with 400 mg. stat of phenylbutazone, followed by 100 mg. every 4 hours until all evidence of acute joint inflammation resolves. This, in our experience, rarely requires more than 4 days and no evidence of toxicity has been observed.

Observation in 11 cases of the serum phenylbutazone level, at the time when significant relief of joint pain occurred, will be presented. These serum phenylbutazone levels ranged from 2·1 to 3·9 mg. per cent. regardless of the dosage schedule. These levels are insufficient to cause uricosuria.

Renal and Anti-Inflammatory Effects of Phenylbutazone Metabolites and Derivatives in Gouty Subjects. By T. F. YÜ, B. C. PATON, J. J. BURNS, J. M. STEELE, B. B. BRODIE, and A. B. GUTMAN, *New York, N.Y.*

New phenylbutazone derivatives are being synthesized in an attempt to develop a drug retaining the anti-inflammatory and uricosuric properties of phenylbutazone, but with fewer undesirable effects. After preliminary screening, five of these compounds were studied. The anti-inflammatory effects were observed in acute gouty arthritis (25 cases), and simultaneous renal clearances were measured in interval gout (33 cases).

None of these compounds substantially alter the inulin clearance, all depress PAH clearance.

G-25671, the phenylthioethyl analogue of phenylbutazone, may be useful clinically; it has moderate anti-inflammatory activity and a very marked uricosuric effect, with minimal sodium and water retention.

G-25903, the phenylthiopropyl analogue, has little anti-inflammatory effect and only mild uricosuric action.

G-13838, the isopropyl analogue, causes transient uricosuria and marked sodium retention, and has no anti-inflammatory effect.

Two of the compounds are metabolites recovered from the urine of patients receiving phenylbutazone.

G-28231, the β-hydroxybutyl derivative, is not antirheumatic but has marked uricosuric and very little sodium-retaining effects.

G-27202, the p-hydroxyphenyl derivative, has the potent anti-rheumatic activity of the parent compound and a rather mild uricosuric effect, and causes rapid and marked sodium retention.

The studies demonstrate that the anti-inflammatory, uricosuric, and sodium retention effects of phenylbutazone can be dissociated by appropriate alterations in molecular structure.

Discussion.—DR. L. MAXWELL LOCKIE (*Buffalo, N.Y.*): Has Dr. Huffman had the opportunity of studying similar cases in which colchicine was administered at the same time as the phenylbutazone? It was our impression at Buffalo that if colchicine were given in small doses such as 0·5 mg. with a 200-mg. dose of phenylbutazone every 2 hours for three or four doses, that the response was very prompt and lasting.

DR. HUFFMAN: We have made no attempt at comparing colchicine with this substance.

DR. ARTHUR I. SNYDER (*New York City*): Has Dr. Huffman given any consideration to the duration of attack before beginning direct therapy, and to the therapeutic response at various dose levels?

DR. HUFFMAN: A number of the attacks had gone on for 5 to 6 days before we started therapy. The Butazolidin was then effective in those instances, but perhaps the response was slower.

DR. JOHN BURNS (*New York City*): It was pointed out that phenylbutazone had both a phenolic compound and an alcohol derivative. We are interested in the phenolic compound because here we have one which is metabolized by the introduction of a phenolic group into phenylbutazone which stays in the body as long or possibly longer than Butazolidin. In fact, we are able to detect considerable concentrations of the compound in the plasma level of about 30 mg. per litre of metabolic concentration, where Butazolidin occurs at about 100 mg. per litre. At present we are working to see whether this particular compound could mediate part of the action of the phenylbutazone itself in anti-inflammatory effect and sodium exclusion.

DR. J. NORRIE SWANSON (*Toronto, Ont.*): Were any toxic effects of Butazolidin encountered during the short-term therapy employed, and were there any patients whose attacks of gout did not respond to Butazolidin?

In Toronto, we have a series of gouty patients comparable in number to Dr. Wilson's. Four patients did not respond to Butazolidin after receiving 600 mg. daily for 4 days, but then responded rapidly to intravenous colchicine, some relief of pain being noted as early as half an hour after injection. One injection of 3 mg. colchicine intravenously is frequently, in our opinion, of greater and more rapid benefit, without nausea or vomiting, than 1 oral dose of 600 mg. Butazolidin.

DR. HUFFMAN: We have had no failures, though we are aware that others have, and we have had no serious toxic effects. We have given doses of 800 mg. to eighteen patients, some for the purpose of obtaining serum levels and others for therapeutic reasons. Approximately six of these patients noted a little stomach distress after receiving the single large dose, but in no other instance have we had toxic effects that could be ascribed to the drug. One patient vomited his 400-mg. dose, but later that day was discovered to have an intestinal obstruction for which he was intubated, and later on, he was able to tolerate the same dosage very nicely.

DR. YÜ: In carrying out the previous studies, we encountered skin rashes in two cases after G-26571. One of the two subjects had a similar hypersensitivity to phenylbutazone.

DR. J. J. BUNIM: Will Dr. Yü tell us how she evaluates any kind of inflammatory effects?

DR. YÜ: The anti-inflammatory effects were evaluated in patients with acute gouty arthritis. All the observations were made by the same person. I usually recorded the degree of inflammation the day before I started the treatment, noting the degree of swelling, redness, heat, limitation of motion, and tenderness. Then I gave the medication, and after 24 hours examined the patients again for signs of inflammation. Complete response obtained in from 24 to less than 48 hours was considered good. Any response which took place only after 48 to 72 hours was considered fair. If they still had some sign of inflammation after 72 hours I considered the response to be poor. Any that do not respond after 96 hours, I considered as entirely negative.

* * * *

PANEL DISCUSSION

(MODERATOR: DR. ALBERT J. KEY)

Reconstructive Surgery in Arthritis

Prevention and Control of Arthritic Deformities in the Hand. By JAMES E. BATEMAN, *Toronto, Ont.* (By invitation.)

In the rehabilitation of the upper extremity, emphasis should be placed on the function of the hand. The management of the deformities resulting from arthritis requires prevention as well as correction, and the two are complementary.

Splinting is the most effective measure in preventing deformity and constitutes a real challenge in the rheumatoid hand. To be useful to arthritics a splint must be simple and flexible. It must control the deformity yet not produce pain nor irritate sensitive parts. It should be light, easily moulded, yet durable. These requirements have been met by the development of a new splint which has worked most effectively. The apparatus consists of a forearm and wrist chassis to which the finger controls are added. Individual springs regulate the fingers while deformity of the hand as a whole is controlled by a master spring. The corrective parts are kept on the dorsal surface so that the palm is free. In this fashion use of the hand as a whole can be encouraged. The splint is made to measure and so constructed that it may be worn for years if necessary.

Established deformities requiring surgical correction arise in all forms of arthritis, but chiefly in post-traumatic and rheumatoid lesions. In the wrist the most effective procedure to correct deformity and prevent pain is arthrodesis. It is recommended that fixation extend from the radius to the base of the metacarpal so that all deforming factors are controlled. A modified Brittan type of arthrodesis has proved most satisfactory.

Deformity in the fingers is a difficult problem for many reasons. Only limited use may be made of arthrodesis because of the infinite demand for varied positions of the digits. Efforts, therefore, should be toward some form of arthroplasty. In a non-weight bearing joint the possibility of replacement arthroplasty is most attractive. To this end a vitallium prosthesis has been used in interphalangeal arthroplasty. The technique is to resect the damaged joint surface, usually the proximal segment, and to replace the whole tip of the phalanx. This results in a stable joint, but leaves a considerable degree of controlled movement without pain.

Discussion.—DR. J. NORRIE SWANSON (*Toronto, Ont.*): If one considers in a little more detail, how the deformity arises, one may arrive at a different conception of splinting. I believe the most important factor in the production

of deformity is muscle spasm. As has been shown by Kellgren of Manchester, England, and Gardner of Detroit, as soon as there is pain in a joint, the adjacent muscles are thrown into spasm to prevent movement. Although the spasm is protective to the joint, it is eventually destructive to the muscle itself. It follows, therefore, that one of the first things to be dealt with in the prevention of deformity, is to *relieve* the spasm. Anything, however, that *increases* the spasm is, I think, wrong: I do not believe that to put the fingers in a spring splint as Dr. Bateman suggests, is resting them. That is increasing the tension, and so will increase the spasm, thereby aggravating the pain, and perhaps even making the arthritis worse. It is not the right thing to do in the active stage of the disease.

Later, when the disease activity has decreased and it is soft tissue contracture that is responsible for the deformity, it may be right to use this type of splinting. But until then, the hands should be rested comfortably in the usual plaster of paris, or another type of plastic splint, so that the pain is relieved. The spasm will nearly always then disappear. This is a quicker, more comfortable, and more physiological way of relieving spasm, or of preventing or treating early deformity.

Then, again, I do not think it is very easy to wear a splint with springs during the night. However, I do not wish to detract from the usefulness of Dr. Bateman's paper as a whole.

DR. BATEMAN: Dr. Swanson's observations are very pertinent. Certainly the initial disturbance is one of spasm, but I have never been able to assess and decide when that spasm passes into the deforming stage of shortening. Electromyelographical studies show disturbed electrical potentials indicating spasm, but after a while that spasm goes, and the muscle is shortened, though it looks the same on the outside. I was speaking primarily of correcting the later well-established deformities, but if we could decide when the so-called spasm becomes shortening, we should be able to control these deformities much better.

DR. CURRIER MCEWEN (*New York City*): Could Dr. Bateman enlarge on the role of exercises, and also on arthroplasty without prosthesis in the correction of deformities of the hand?

DR. BATEMAN: Exercises, voluntary movements, have a place in the whole programme. A hand will be encouraged to exercise if it is kept in the position of function and free of obstructive apparatus. It is difficult to encourage the use of a hand that splinted by something that blocks the normal grasping tendency.

Once the deformity is reasonably well controlled, I think that exercises can be used perhaps without the splint, but the spring splint in itself is an exercise apparatus. The coil spring at the base produces an obstruction and helps to control flexion so that the flexures can work against it.

On the question of arthroplasty apart from replacement arthroplasty, many early contributions on arthroplasty, particularly in rheumatoid arthritis have been made. The principle of replacing the damaged area is most attractive because it allows us to correct the deformity completely and then we start off with a good joint surface to initiate movement.

As a general principle, particularly in rheumatoid arthritis, arthroplasty is not yet sufficiently well developed to be considered.

DR. DONALD F. HILL (*Tucson, Ariz.*): How many patients have worn these splints, and for how long? Have you evaluated them after prolonged use?

DR. BATEMAN: We have applied these splints in between 75 and 100 patients, and some have worn them for 3 or 4 years. We have no well-organized follow-up on the exact degree of deformity corrected, but the important thing is that these patients are sufficiently improved from the start to become used to their splints and to be content to use them for a long time. Some patients have even gone back to work using their splints.

MODERATOR KEY: Do they sleep in them, too?

DR. BATEMAN: Yes.

DR. ROBERT S. HORMELL (*Boston, Mass.*): We, too, have used spring and rubber elastic splints in the treatment of rheumatoid deformities, but without much success. Under our best directions the deformities progress relentlessly while the patient is using the splints and doing his exercises. Perhaps our splints have not been used long enough or often enough because of discomfort or difficulty in their application. We suspect, however, that the reason for continued progression while under treatment is that adaptive changes in the epiphyseal portions of the bones progress, even in the absence of activity of the rheumatoid process. We feel that these adaptive changes are the response of the bone to the static and kinetic forces of gravity and of muscular pull on the bones and joints.

Dr. Bateman's splint includes a snap fastener device, which is very neat and very necessary. Buckles and other fasteners are not so suitable as this simple fastener, which the crippled rheumatoid can remove with ease. Where can this snap fastener be obtained?

DR. BATEMAN: I do not think elastic traction is good enough in correcting these deformities. It is not steady enough, you cannot adjust it to the exact degree which is required, and as the deformity improves, you cannot continue to correct it.

The most serious deformities of severe atrophic arthritis, telescoping of the fingers, and so on, may be prevented if the initial lesion is treated properly. If the metacarpal phalangeal joint is kept as close to the mid position as possible, the interossei are not able to shorten and so produce the severe telescoping.

These splints have been made in our limb factory at the Department of Veterans Affairs in Toronto, and also by brace makers in the city.

DR. ABRAHAM S. GORDON (*Brooklyn, N.Y.*): Is Dr. Bateman familiar with the splint for the ulnar deviation deformity that I described a number of years ago? This consists of a simple glove made out of tough but thin material—similar to that used for elastic stockings. The glove is made to measure from the middle of the forearm to, but not including, the terminal phalanges of the hand. At the thumb, which is not involved in the deformity, the glove is cut down to the base of the metacarpophalangeal joint. This permits the free use of all fingers while the glove is worn. For the entire length of the glove, half-inch wide tapes are sewn on the ulnar side and on the dorsal and ventral surfaces at the ring finger, and into these tapes are inserted thin steel bars, about $\frac{3}{8}$ in. wide. These are somewhat flexible, but firm enough to correct the deformity. Then a longitudinal cut is made on the ventral surface from the end of the glove at the middle of the forearm to a point about the centre of the palm, and a zipper is sewn into the opening. With the zipper open the glove is easily put on by the patient, and when it is closed the deformity is straightened.

This is a very simple type of splint and I have had quite a few of them made. The patients like it very much and they can sleep with the gloves on without any discomfort. The steel bars may be slipped out of the tapes for washing.

Reconstruction of the Knee in Rheumatoid Arthritis. By ROBERT L. PRESTON, *New York, N.Y.*

Inspection of disabled joints at operation reveals that the most characteristic features of the deforming pathology of rheumatoid arthritis are the soft tissue changes in and around the joints and in the muscles, fasciae, and skin. In most instances, the pathological changes in bone and cartilage do not cause disability.

Musculo-skeletal disability due to soft tissue pathology often can be prevented by protection of inflamed joints from trauma, prevention of deformities, and the restoration of strong and accurate muscular control by means of corrective exercises.

However, if fixed deformities are permitted to develop, the soft tissue pathology is still amenable to correction, but extensive reconstruction is usually required.

If function is to be restored to a severely disabled knee, an operation must be done which is extensive enough to correct all the principal features of the deforming pathology. The contracted tissues must be lengthened so that the knee can be brought into full passive extension. The intracapsular causes of impaired active and passive motion in the anterior compartment of the joint must be eliminated by excision of scar, removal of the irregularities of the articular surfaces, and restoration of adequate intracapsular space. Physiological tension must be restored to the overstretched extensor motor apparatus so that the scarred and atrophic extensor muscles can work at maximum advantage to move the joint into the weight-bearing position.

In all except the rare case in which the bony degeneration is so severe that a stable, painless joint will not result from any procedure except fusion, the objective of the operation is a knee which can be moved painlessly through at least the minimal range necessary for ambulation. This objective is achieved in many cases.

Discussion.—DR. MORTIMER ELKINS (*Hampton, Va.*): What are Dr. Preston's views on further attempts at rehabilitation of a contracted knee? We had two patients with rheumatoid arthritis with flexion contraction of the knees, and by using plaster casts we straightened the knees sufficiently for the patient to walk on metal bar splints.

What does he feel about the medical attempt to rehabilitate the knees?

DR. PRESTON: I don't like the use of wedged casts in these cases because if the scar tissue surrounding the joint is extensive and the contractors are firm, complete correction of the deformity cannot usually be accomplished and the disability almost invariably recurs.

Stretching by any means, either by wedged casts, traction, or under anaesthesia, should be limited to cases in which the contractures are slight and the adhesions fragile, in which the pathology is more severe than can be handled by corrective exercises.

Cutting the scar and the contracted tissues and cleaning up the joint in a surgical operation restores a greater degree of free motion, and this type of procedure is not so liable to be followed by post-operative recurrence.

DR. RICHARD A. FREYBERG (*New York City*): Dr. Preston has given an excellent exposition of the nature of the deformity and the practical means of correcting anatomical abnormalities. We who have to deal with these deformities fully appreciate that after the surgeon has made such successful reconstructions, a prolonged programme of functional rehabilitation is required.

Has Dr. Preston found systemic steroid therapy or local intra-articular hydrocortisone useful in either pre-treatment or post-treatment?

DR. PRESTON: We should like very much to instill local hydrocortisone at the time of surgery but we have never been able to figure out how to use it, because at the completion of the operation there are so many openings in the joint that it would leak out. As soon as we possibly can, we start both local and systemic hydrocortisone.

These steroids make it easier to rehabilitate these patients post-operatively. I know that there is some difference of opinion as to whether they actually cut down scar formation post-operatively, but from the practical standpoint, observing many of these cases, I feel that they must do so, because in the cases in which the steroids are used we have less trouble in securing the functional result and the entire situation is much more favourable.

DR. JOHN W. SIGLER (*Detroit, Mich.*): What procedure was employed in the first case Dr. Preston presented?

DR. PRESTON: In both cases the three-phase reconstruction operation was done. Phase 1 consists of posterior capsulotomy and lengthening of all the tissues on the flexor side of the joint; everything except the nerves and vessels. In Phase 2 the anterior aspect of the joint is opened for the correction of any pathology which will interfere with the active motion of the joint. In Phase 3 the slack is taken out of the extensor motor apparatus if it is too lax.

DR. CURRIER MCEWEN (*New York City*): The question of wedge casts was raised a few moments ago. I think wedging is a dangerous procedure; that if the correction cannot be achieved by less traumatic means than wedge casts—that is, by simple exercise and perhaps mild stretching under anaesthesia, followed by some traction—it is far better not to try to wedge but to move right on to an open operation.

In the patients whom I have had an opportunity to follow, it seems to me that every time we tried wedging, we got into a worse situation than we had before.

DR. DONALD F. HILL (*Tucson, Ariz.*): I heartily agree with the last statement, that mild procedure is fine; rather than use too much force, surgery will do a neater job with less trauma. We have seen much improvement in our knee operations in the last 5 years.

What did Dr. Preston do with the lower ends of the femur after reshaping it? Was fascia used as a lining?

DR. PRESTON: Only one element of the joint, the lower end of the left femur, was left covered with raw bone. Inasmuch as the opposing element, the tibia, was covered with scar, pannus, and some articular cartilage, it was not necessary to put in any membrane. Interposing a membrane is only required when two opposing surfaces will be raw.

DR. BERNARD M. NORCROSS (*Buffalo, N.Y.*): What dose do you use in the knee joint? It has been our experience that putting in doses of 250 and 300 mg. makes a significant difference and the effect lasts longer.

DR. PRESTON: We have not been using dosages higher than 75 to 100 mg.

DR. THEODORE A. POTTER (*Boston, Mass.*): The type of case that Dr. Preston has explained to-day is probably entirely different from the arthritic joints that we see in Boston. The type of joints we see have extensive intra-articular damage of bone and cartilage, and such procedures are only suitable to very few.

We call this the joint débridement and it works very well in the osteo-arthritic patient, but in our hands is most unfavourable in the rheumatoid arthritic. In a severely damaged joint, we have two procedures to choose from: fusion or arthroplasty.

In the very mild cases, serial applications of casts is sufficient to straighten out the knee joint, provided there is not intra-articular damage.

MODERATOR KEY: Is Dr. Paul Holbrook here? I learned something from him about 20 years ago about the knees. I have refrained from making remarks, but silence does not mean consent on my part to either of these papers.

Paul, you tell them about your excellent results with repeated manipulations under anaesthesia.

DR. W. PAUL HOLBROOK (*Tucson, Ariz.*): Concerned at the endless bent knees of our long-term chronic patients with rheumatoid arthritis, we began studying the orthopaedist's methods, in trying to correct flexion contractures of the knee.

We felt, and still feel, that a straight knee is better than a bent knee. The earlier you can straighten the knee, the better it will be, regardless of the general activity of the disease. The longer the knee is bent, the more difficult it will be to straighten, and the more intra-articular damage will occur.

We did a large series of manipulative corrections under anaesthesia, sometimes not getting a complete straightening in one stretching and having to do it again, being as gentle as we could and yet bold enough to try to succeed in straightening the knee.

Out of more than 100 which we had done up to 10 or 15 years ago, about seventy or more are walking, and have maintained straight legs after manipulation.

This is not to say that bad knees ought not to have surgical intervention, and we now have enthusiastic and co-operative orthopaedists who help us a great deal with the bad knees. We still feel that we can readily and quickly straighten the easy ones early in the disease.

MODERATOR KEY: Dr. Preston, you have one question to answer about the difference between arthritis in Boston and New York.

DR. PRESTON: In certain cases there is too much intra-articular bony pathology to expect a painless, stable knee to result from any procedure except fusion. But, as the years pass, this group, in New York, has been getting smaller, so that to-day the three-phase reconstruction operation is used on three out of four of the cases which, before the war, we should have fused.

DR. EDWARD W. BOLAND (*Los Angeles, Calif.*): We have all profited greatly in hearing *how* reconstructive operations for the knees in rheumatoid arthritis may best be performed. There are many of us here, I am sure, who are just as interested in *when* such procedures should be undertaken in relation to disease activity as it affects the disease in general and the involved joints in particular.

DR. PRESTON: I don't think that the sedimentation rate or other evidences of systemic activity need to be considered too seriously. What is important is the severity of the rheumatoid activity in the joint which is to be treated, which isn't necessarily the same as the level of the systemic rheumatoid activity.

Of course, it is undesirable to do an extensive surgical correction on a joint that is the seat of acute rheumatoid inflammation, but with this exception, I feel that these joints should be operated promptly. I see no reason for waiting for years for the disease to "burn out". The end-results of cases which operated while the disease was active do not indicate that this delay is necessary. By rehabilitating the patient promptly, years of invalidism is avoided.

MODERATOR KEY: I would go further than that, and say, do it as soon as you can get the patient's consent. The earlier you do it, the less surgery you have to do, and the better your result is going to be, provided you can continue after-treatment and prevent a recurrence.

Frank Dixon used to feel (and I imagine he still does, and I think he has good grounds for it) that operating on these acutely affected joints sometimes arrests the progress of the disease, just as they used to take tonsils out and cure rheumatoid arthritis—or at least get a remission, probably through a change in the physiology of the individual resulting from the anaesthetic and the surgery.

I do not feel that you should wait until the arthritis is cured, because by that time the patient may be amenable to help but not to correction.

Reconstructive Surgery of the Hip in Arthritis. By CARL E. BADGLEY, *Ann Arbor, Mich.* (By invitation.)

Reconstructive surgery of the hip in arthritis produces at its best a poor substitute for a normal functional hip, but many procedures have been helpful in alleviating pain and diminishing disability.

Extra-Articular Procedures have been many and varied. Correction of flexion and adduction contractures by soft tissue release and by osteotomies have temporarily benefited for short or occasionally long periods. Forage of the neck and head of the femur has improved some cases sufficiently to encourage some clinicians. Others have tried to de-nervate the hip joint.

Intra-Articular Procedures. Acetabuloplasty and cheilectomy have not been successful with sufficient frequency to warrant their use. Pseudarthroses of the hip relieve pain, but with considerable loss of function. Arthroplasties of the hip or the substitution for the head and neck of the femur of a mechanical prosthesis have been successful in some. Arthrodesis of the hip with fusion is most successful for standing and walking, but difficult for sitting.

Discussion.—MODERATOR KEY: The single most useful therapeutic measure in osteo-arthritis of the hip is to persuade the patient to use a walking stick and rest the hip, and the older I get and the more I see of the hips I have operated on to restore movement, the fewer operations I recommend. Dr. Badgley has shown a good one, and I have a few good ones too, but I have a lot more poor ones. We don't show those, but they show themselves to us, and we cannot always be sure that the patient is going to be better when you have finished than before you started.

Weight reduction and exercise are also important.

Hydrocortisone Injected into Degenerated Intervertebral Disks. By HENRY L. FEFFER, *Washington, D.C.* (introduced by J. J. Bunim).

Although degeneration of the intervertebral disk is an insidious process beginning in the second decade of life, acute clinical episodes are probably associated with sudden increases in intranuclear pressure. Protrusion of the disk thus is governed by the fluid balance within the nucleus pulposus, and symptoms are produced by tension on the posterior longitudinal ligament and adjacent spinal nerve roots.

In view of the universally accepted value of intra-articular hydrocortisone therapy in degenerative joint disease, it was felt that the drug should have a similar anti-inflammatory action on the intervertebral disks. Sixty patients with suspected disk disease as well as controls were treated by combining a nucleogram with the injection so that all results could be interpreted in the light of the pathology illustrated.

Of the sixty patients, 55 had pathological disks and in 37 (67 per cent.) rapid remission was achieved. The response has been permanent in all but four for a maximum follow-up period of 8 months. Sixteen of the eighteen patients who were not relieved were surgically explored, and all demonstrated gross ruptures through the annulus fibrosus.

Discussion.—DR. THOMAS MCP. BROWN (*Washington, D.C.*): I think we are all interested from several points of view. Sometimes conservative measures may be worth while, and at other times we should advise early operation to avoid permanent difficulties.

Finally, we recognize those cases in whom the disease is apparently present, at least in whom the herniation is obviously present in the myelogram, who at operation reveal very little; some of these individuals later experience great back pain, possibly to some degree furthered by the operative procedure.

The most important thing presented by Dr. Feffer is a diagnostic tool to separate these two groups.

From the therapeutic point of view we have the interesting fact that a single injection will do so much good; this separates this group from those with peripheral articular involvement requiring repeated injections.

Has Dr. Feffer any plans to study the pathophysiology of the alteration induced by this single-injection method?

DR. FEFFER: Dr. Brown, physiologically, the intervertebral disk encloses a gel confined within the annulus fibrosus. It swells as the gel swells by inhibition in response to stresses and strains, and shrinks when those strains are relieved.

The swelling of an intervertebral disk in the pathological state is evidently different and is related to the drawing in of surrounding fluid through the cartilaginous end-plates because of an increased osmotic pressure within the disk. This is probably a depolymerization effect and since the chondroitin sulphate, which is the predominant polysaccharide in the nucleus, is extremely sensitive to the slight changes in *p*H, I am trying to figure out, at this time, an electrode which would make *in vivo* studies feasible. This might give us more insight into the actual nature of the pathological physiology than any other form of investigation.

DR. WILLIAM H. GOODSON (*Kansas City, Mo.*): Were myelograms made before the injection?

DR. FEFFER: The severe ones had only nucleograms or discograms, and most of us feel these are routinely more accurate than the myelogram, which produces about 20 per cent. false negatives. There were some with negative myelograms who continued to have a typical clinical disk picture. When these were subjected to that procedure a good percentage showed a degenerated or herniated disk.

DR. J. ALBERT KEY (*St. Louis, Mo.*): If this work can be substantiated, Dr. Feffer has certainly made a very important contribution to the low-back problem. We do not cure all those we operate on by any means, and he achieves nearly as many cures as we do. I do not know how many patients are benefited to a point where life is more tolerable. Such patients are extremely important because those that we fail to help are usually the ones that this procedure does help. Apparently, by this method, we may be able not only to diagnose them beforehand, but also to cure a high percentage of those which we have not been able to cure by surgery.

We tried the discogram about 2 years ago. We used a 26-gauge needle, which is the one recommended, and we had such a hard time doing it that we gave it up. Dr. Feffer is bolder and uses a bigger needle, and I think maybe I can go home and try again.

DR. FEFFER: Dr. Key's comments brought to mind the subject of recurrences. I have recently heard of a patient who was operated upon by a neurosurgeon without his knowing that I had been in the picture before. I had injected only the fifth lumbar disk which was degenerated, and the patient had recovered, but 3 months later he had a recurrence, and on exploration the recurrence was found to be at the level of the fourth lumbar disk. The fifth was normal. This proves that the vagaries of the whole disk picture with its multiplicity of involvement can confuse diagnosis and ruin the surgical result.

* * * *

Rehabilitation of the Arthritic Hand. By RALPH A. JESSAR and ERNEST M. BROWN, JR., *Philadelphia, Pa.*

Since disabilities of the hands of the rheumatoid arthritic patient are the results of inflammatory involvement of the small joints and soft tissues and tendons of the hands, an attempt was made to develop a technique whereby the disability and deformity might be reversed or arrested. The following sequence of events represents the pathogenesis of the hand deformities:

(1) Inflammation of the small joints of the fingers with the resultant joint effusion and distension.
(2) Prolonged joint effusion and concurrent distension allows stretching of the ligamentous fibrous tissues of the joint with subsequent subluxation.
(3) Subluxation is maintained by the muscles of the flexor groups.
(4) Flexion contractures occur and are maintained by a secondary stenosing tenosynovitis affecting the flexor muscle tendons.
(5) Concurrent inflammatory involvement of the hand muscles leads to atrophy and disuse promoting further hand deformities.

Since these hypothetical changes might be susceptible to modification or reversal, an attempt was made, using intrasynovial hydrocortisone, infusion and distension of

the flexor tendon sheaths of the hands, and intensive physiotherapy, to rehabilitate the involved hands of a limited number of rheumatoid arthritics. In a small number of patients it has so far been possible to correct, at least partially, acute ulnar deviation, early spindle-shaped deformity of the proximal interphalangeal joint, "grasshopper deformity" of the fingers, and stenosing tenosynovitis of the flexor tendons. As a result of these studies, it is believed that if sufficient attention is paid to the reversibility of early inflammatory lesions of the joints, tendons, and soft tissues of the hands in rheumatoid arthritis, late deformities and disabilities may be for the most part prevented or corrected.

Osteo-Arthritis of the Cervical Spine. Stages and Treatment. By JOHN G. KUHNS, *Boston, Mass.*

Symptomatic osteo-arthritis of the cervical spine is found in about 10 per cent. of the patients seen in an arthritic clinic. Usually the disease shows gradual progression both in pathological changes and in symptoms. Three stages can be recognized: early, moderately advanced, and late. In the early stage the symptoms are usually those of muscular sprain, and treatment chiefly consists in support and physiotherapy. In the moderately advanced stage the symptoms are usually neurological in character, and symptoms are relieved by traction on the cervical spine, firm support to the neck, and relief of pressure upon the nerve roots by surgery. Displacement of degenerated intervertebral disks is rarely demonstrated, although gradual disappearance of the disks is common. In the late stage, irreversible changes are frequently found in the cervical spine, and symptoms are usually both mechanical and neurological. Three types of end-stage are observed: bony bridging with extreme limitation of motion, forward subluxation of a cervical vertebra with disappearance of the cervical intervertebral disk, and osteoporosis with vertebral collapse. Treatment is symptomatic, usually consisting in rigid support of the cervical spine.

Discussion.—DR. W. K. ISHMAEL (*Oklahoma City, Okla.*): Has Dr. Kuhns any observations on the occupation of patients with severe symptoms from degenerative arthritis of the spine. A recent resident in our clinic from Calcutta, India, became quite interested in the high increase of back symptoms in our rather "lightly laden" clientèle. He, therefore, studied a group of Hindu porters in Calcutta by careful history and *x*-ray studies of the spine. He found that none of these porters had ever had pain referable to the spine—not even a "pain in the neck"!

In a similar study of our cases, for every common labourer who has come to the Arthritis Section with pain in the back, there has been at least one physician.

DR. KUHNS: There is no direct correlation with occupation. People who sit and bend over are affected much more frequently than those who live their lives in a more erect position. This we have thought was the result of posture or static stresses and less good muscular development in the antigravity muscles of the neck.

DR. STEPHEN J. WALKER (*Whitesboro, N.Y.*): During the past 15 years I have seen a great number of cases of osteo-arthritis of the cervical and lumbar spine, and have treated them on the same principles as Dr. Kuhns.

I should like to bring to your attention a product, which has not yet found its proper place in our armamentarium, called Endogen A*. I started using it in the 1920s and it has done wonders for the majority of these patients ever since.

Nobody seems to know exactly the rationale of the effect of Endogen A, although the role of casein and peptone as well as colloidal sulphur is obvious. I have always used it in conjunction with salicylates, and, more recently, with Butazolidin in the therapy of most forms of osteo-arthritis. In the early stages of the disease I give one ampoule twice a week and reduce the dosage gradually to one ampoule weekly until the patient's condition is definitely improved. All other supportive measures, such as diet, rest, and an optimistic outlook for the future are equally important in treatment.

DR. KUHNS: I have observed temporary improvement after injections of a number of substances. A number of my medical colleagues will give oestrogens, or testosterone, and in most instances the patients become temporarily better. There are many physiological and metabolic factors in this disease which we do not understand.

DR. PHILIP R. TROMMER (*Philadelphia, Pa.*): Why does cervical traction sometimes aggravate the condition?

DR. KUHNS: I have observed this phenomenon, but I do not know that I can give you any definite answer.

There are many ways of giving traction. I have been surprised that nobody has brought me to task for not giving heavy intermittent traction in the upright position. There are many other ways; some of my colleagues give it at 45°. When our type of traction does not work, we usually change the direction of the pull, feeling that we are not relieving the pressure by the supine position.

DR. PHILIP R. TROMMER (*Philadelphia, Pa.*): I am reminded of an answer that was given at the last Congress of Physical Medicine in Washington. They pointed out that the spurs came from the neuro-canal pointing downwards, and that when you put traction up it made the angle much larger.

They pointed out that the nerve canal is like a sleeve. You have a spur here and if you pull on the nerve and put traction up here, you are aggravating the situation.

I have tried it on some by stretching the neck by hand; if that makes them worse, we do not use traction.

Controlled Therapy of Degenerative Arthritis. By EUGENE F. TRAUT and EDWIN W. PASSARELLI, *Chicago, Ill.*

The various forms of chronic arthritis have a fluctuating natural history characterized by remissions, relapses, and progression. The importance of the psyche in the pathogenesis and course of arthritis is increasingly apparent. On these accounts and to satisfy the natural desire of the patient to initiate treatment at his first visit, we decided to fashion a base line by placebo therapy. Besides serving as a control on effects of other measures, placebos would not interfere with such laboratory procedures as measurement of the uric acid level in the serum, the sedimentation rate of erythrocytes, or the various serological tests. The placebo procedures instituted were lactose tablets and subcutaneous injections

* Manufactured by Endo Products, Inc., Richmond Hill, N.Y. It is available in 2-ml. ampoules containing a solution of 50 mg. casein, 60 mg. peptone, and 5 mg. colloidal sulphur.

of saline. The tablets were exhibited first. If the patient failed to be improved by tablet placebo or was benefited initially only to fail to improve later, the injection placebo was instituted. The patients were interviewed and examined as to their progress by six rheumatologists, each being careful to maintain a casual, non-suggestible attitude. The results were described by the patients and also obtained by inquiry and by physical and laboratory examination. Data were broken down according to race and sex.

Over 182 patients with degenerative arthritis were studied in this manner for one and a half years. More than half of those receiving lactose tablets experienced relief, justifying continued visits to the clinic and the abandoning of previously used salicylates and proprietary preparations. Those initially unresponsive to tablets and those eventually ceasing to improve on tablets were treated by subcutaneous injections of normal saline solution. Approximately the same percentage of the patients not helped by tablet medication responded favourably to the salt-water injections. There was a sex and race difference in placebo response, and the difference in severity of joint involvement also affected the response. The combined tablet and injection procedures satisfactorily helped significantly 75 per cent.

The conclusion is drawn that such a controlled placebo study is necessary in determining the fitness of newly-proposed treatments to enter our already too large pharmacopoeias and textbooks.

Discussion.—DR. OTTO STEINBROCKER (*New York City*): Any effort to control therapy is a very commendable procedure. I was not able to tell from this interesting discussion whether any attempt was made to correlate the patient's symptoms and the objective findings. I would state from our own experience with so-called osteo-arthritis that it is important to establish the diagnosis on the basis of clinical signs as well as on *x*-ray appearances and the patient's complaints.

It is pretty widely accepted now that there are placebo reactors, and I think the information presented can be valuable if it is correlated with the clinical evaluation of the disease itself as well as with the symptoms.

DR. TRAUT: The correlations mentioned were made, and due observations and findings were recorded. The subjective complaints were relieved in a larger measure than the objective findings. It is quite remarkable that an individual would come in who could not raise his shoulder, and that after a placebo he might move his arm freely. This motion was helpful as spasm was lessened.

Resorptive Osteopathy in Inflammatory Arthritis. By MURRAY SILVER and OTTO STEINBROCKER, *New York, N.Y.*

Atypical clinical pictures of arthropathy in different forms, based on extensive destruction or mutilation of bone, have been described in sporadic reports for many years under a variety of confusing names, such as "arthritis mutilans", "absorptive arthritis", and "opera-glass hand". Five cases with inflammatory arthritides associated with great resorption of bone, two with biopsies of articular structures, provide the material for this report. They suggest the need for a better understanding of this unusual manifestation of the arthropathies.

That such lesions do occur in different forms and in almost any site is another reflection of the diverse nature of the arthritides. These bone lesions may simulate other pathological processes, particularly cysts and neoplasms. They may baffle the radiologist and clinician if it is not recognized that single or multiple bones may be extensively resorbed in a variety of ways and degrees in the inflammatory rheumatic disorders. Similar changes, which have received little attention, may be encountered in degenerative lesions of joints and bones.

Our series includes three types of radiological alteration. In the first there may be seen resorption of as much as one half to a whole phalanx, or multiple phalanges. One or more of the carpal bones may be affected alone, or in addition to the phalangeal changes. The classic example of such marked bone resorption involves the fingers to produce the "opera-glass hand", or the telescoping of the phalanges of one or more digits. In the second type, the long bones are involved with small and large osteolytic lesions, cyst-like in some instances, at times extending into the marrow. In the third form, there may be tapering and disappearance of large portions of the long bones, a diffuse resorption, retaining a striking and nearly uniform architecture of the residual bone, with a peg-like appearance at the affected portions. These alterations may occur in multiple forms in some cases.

The non-specific nature of the pathological process is described. Of our five cases, one suffered from psoriasis with arthropathy, one from ankylosing spondylitis with root joint involvement, and the others from rheumatoid arthritis.

Discussion.—DR. SWIFT (*Chicago, Ill.*): I am very much interested in the first case that was presented and I wonder if this patient had psoriasis. We have a case in the ward of an elderly woman who has had psoriasis of the elbows for years, with a telescopic thumb.

Another observation of interest is that a case has recently come into our out-patient clinic which looks like advanced osteomyelitis. On *x* ray, the similarity was striking, and this paper warns us to be on the lookout for other diseases.

DR. SILVER: The patient described did not have psoriasis, but there are other cases in the literature in which psoriasis was associated with "opera-glass hand".

DR. CUMMINGS (*Rochester, N.Y.*): Was parathyroid disease ruled out?

DR. SILVER: The calcium, phosphorus, and alkaline phosphatase determinations were normal in these patients. Hyperparathyroidism can thus be ruled out because one would expect biochemical alterations in the presence of bone disease due to this cause.

Dynamics of Normal and Arthritic Joints (cinematic demonstration). By R. H. FREYBERG, E. RUDD, ARTHUR POST, with the technical assistance of W. CARLIN and G. KLOOS.

A recently-developed means of electronic intensification of fluoroscopic images, has made possible a moving-picture demonstration of joints in normal persons and in patients with arthritis as seen with the fluoroscope. The candle power is intensified by 1,000, so that these

films can be made in the same way as *x* rays of the chest and the patient does not receive excessive radiation.

One difficulty involved in making these films is that the size of the field is limited to a diameter of about 5 inches. A knee joint thus just about covers the field and if the movement takes it off the central beam, the fluoroscopic image is lost. One can expose the film at 64 frames a second and show it in slow motion, so that all subtleties show up very exactly.

* * * *

The following papers were also presented but not read:

Long-Term Course of Patients with Rheumatoid Spondylitis treated with Roentgen Therapy. By KEITH H. AVERILL, IVAN F. DUFF, HENRY ZEVELY, W. D. ROBINSON, and ISADORE LAMPE, *Ann Arbor, Mich.*

Effect of Butazolidin (Phenylbutazone) Levels in the Plasma on the Response to Mercurial Diuretics. By HAROLD BROWN and ROBERT S. WARNER, *Salt Lake City, Utah.* (Introduced by John C. Nunemaker.)

Gout in 190 Patients with Emphasis upon Race, Heredity, and Socio-Economic Factors. By HENRICH G. BRUGSCH, MICHAEL G. PIERIK, and JACOB H. YULES, *Boston, Mass.*

Distribution Patterns for Rheumatic Symptoms and Signs. By S. COBB, J. R. ROSENBAUM, J. E. WARREN, and W. R. MERCHANT, *Pittsburgh, Pa.*

Clinical Application of Ivalon Knee Arthroplasty. By MILTON C. COBEY and ANTOINETTE POPOVICI, *Washington, D.C.*

Juvenile Mono-Articular Arthritis; Divergent Form of Rheumatoid Disease. By PAUL H. CURTISS, JR., and RALPH I. WEDGEWOOD, *Cleveland, Ohio.*

Preliminary Clinical Trials with Metacortandracin; Comparative Antirheumatic Potency, Metabolic Activity, and Hormonal Effects. By J. R. DORDNICK and E. J. GLUCK, *New York, N.Y.* (see p. 445).

Spectrophotometric Determination of Antistreptolysin-O. By HARRY A. FELDMAN and ANNE L. GILLEN, *Syracuse, N.Y.*

Treatment of Acute Rheumatic Fever with Metacortandracin. By HARRY A. FELDMAN and LEO JIVOFF, *Syracuse, N.Y.*

Penicillin Prophylaxis in Rheumatoid Arthritis. By PAUL O. HAGEMANN, *St. Louis, Mo.*

Niacin Furfuryl Test and Pathogenesis of Rheumatoid Arthritis. By GEORGE G. HAYDU, *New York, N.Y.*

Correlation of Pain and Radiological Findings of Degenerative Joint Disease of the Cervical and Lumbar Spine. By ALLEN E. HUSSAR and EMANUEL J. GULLER, *Montrose, N.Y.* (Introduced by Howard F. Polley.)

Technique and Rationale for a Routine Comprehensive Physical Examination in Cases of Chronic Musculoskeletal Pain. By J. H. IRVINE, *New York, N.Y.*

Incidence of Positive L.E. Preparations in Patients with Rheumatoid Arthritis. By W. K. ISHMAEL, J. N. OWENS, JR., and R. W. PAYNE, *Oklahoma City, Okla.*

Treatment of Various Rheumatic Conditions with Metacortandracin. By WILLIAM H. KAMMERER and RUSSELL L. CECIL, *New York, N.Y.* (see p. 445).

Treatment of Scleroderma, Sclerodactylia, and Calcinosis by Chelation. By RUBIN KLEIN, *Brooklyn, N.Y.* (see p. 445).

Morphological and Physiological Study of Tissue Cultures of Human and Mammalian Synovial Membranes. By DAVID H. KLING, GLADYS CAMERON, and MILTON G. LEVINE, *Los Angeles, Calif.*

New Methods for the Study of Synovial Fluid in the Diagnosis and Treatment of Arthritis. By DAVID H. KLING and MILTON G. LEVINE, *Los Angeles, Calif.*

Pathology of Experimental Frostbite with particular reference to Cold-Induced Arteritis, Periostitis, and Arthropathy. By J. P. KULKA, J. R. BLAIR, and R. SCHATZKI, *Boston, Mass.*, and *New York, N.Y.*

Effect of Intravenous Colcemide on Acute Gout. By WILLIAM C. KUZELL, RALPH W. SCHAFFARZICK, and W. EDWARD NAUGLER, *San Francisco, Calif.*

Local Cutaneous Response to Nicotinic Acid and Esters as a Diagnostic Aid for Rheumatoid Arthritis. By PAUL LEIFER and ROBERT C. BATTERMAN, *New York, N.Y.*

Studies in Osteo-Arthritis, using Intra-Articular Temperature Response to Injection of Hydrocortisone Acetate. By ROBERT MOORE and JOSEPH L. HOLLANDER, *Philadelphia, Pa.*

Simulated Acute Surgical Abdominal Catastrophe in Systemic Lupus Erythematosus. By VICTOR E. POLLAK, ROBERT C. MUEHRCKE, ROBERT M. KARK, and IRVING E. STECK, *Chicago, Ill.*

Butazolidin. WILLIAM B. RAWLS, *New York, N.Y.* (see p. 444).

Metacortandracin in Diffuse Scleroderma (Systemic Sclerosis). By GERALD P. RODNAN, ROGER BLACK, ALFRED J. BOLLET, and JOSEPH J. BUNIM, *Bethesda, Md.*

Ascorbic Acid and Dehydroascorbic Acid Levels in Plasma in Rheumatoid Arthritis. By MARIAN W. ROPES and MALCOLM THOMPSON, *Boston, Mass.*

Management of Toxic Side-Effects of Phenylbutazone and Cortisone with Emphasis on Ulcer Formation and Water Retention. By DAVID RUML, CHARLES W. DENKO, and DELBERT M. BERGENSTAL, *Chicago, Ill.*

L.E. Phenomenon in Rheumatoid Arthritis. By CHARLES H. SLOCUMB, CLETUS T. FRERICKS, GERTRUDE L. PEASE, HOWARD F. POLLEY, and L. EMMERSON WARD, *Rochester, Minn.*

Joint Changes in Paget's Disease. By IRVIN STEIN and MARTIN L. BELLER, *Philadelphia, Pa.*

Comparison of Rheumatoid Spondylitis and Crippling Fluorosis. By CHARLES LEROY STEINBERG, DWIGHT E. GARDNER, FRANK A. SMITH, and HAROLD C. HODGE, *Rochester, N.Y.* (see p. 378).

Experiences in the Use of Metacortandracin in Disseminated Lupus Erythematosus and Periarteritis Nodosa. By CHARLES LEROY STEINBERG, ANDRIES I. ROODENBURG, and MILTON G. BOHROD, *Rochester, N.Y.*

"Diabetogenic" Properties of Metacortandracin, Hydrocortisone, and Cortisone Acetate—A Comparative Study. By CARL STEVENSON, F. W. MCCOY, and R. H. FREYBERG, *New York, N.Y.*

Rheumatoid Spondylitis: Course and Socio-Economic Significance. By ROBERT L. SWEZEY, JAMES L. PATTERSON, JR., STANLEY MARCUS, JOHN E. MEIHAUS, DAVID A. STRANGE, and MELVIN H. LEVIN, *Los Angeles, Calif.*

Relationship of Sydenham's Chorea to Infection with Group A Streptococci. By ANGELO TARANTA and GENE H. STOLLERMAN, *New York, N.Y.*

Another Concept and Syndrome in Rheumatic Disease. By G. DOUGLAS TAYLOR, *Toronto, Ont.*

Osteogenesis Imperfecta Tarda. By STANLEY L. WALLACE, PHILIP VIGODA, and HOWARD EASLING, *Selfridge Air Force Base, Mt. Clemens, Mich.*

Punch Biopsy of Synovial Membrane of the Knee in Diagnosis of Joint Disease. By HENRY A. ZEVELY, *Ann Arbor, Mich.* (Introduced by Ivan F. Duff.)

BOOK REVIEW

La spondilite anchilosante. By Tommaso Lucherini and Claudio Cervini. 1955. Pp. 469. Edizioni Mediche e Scientifiche, Rome. (L. 4,500; 50*s*.)

This volume of over 400 pages (15 chapters), which is claimed to be the first comprehensive work on ankylosing spondylitis in Italian, has been compiled by the director of the Rheumatological Institute of Rome University and his assistant. Excellent colour-plates, photographs, glossy paper, and an imposing array of indices, all combine to ease the task of the reader. The authors' own experience is based on a study of 215 cases (202 men, 13 women) and results are carefully tabulated. Much industry, too, has gone into the presentation of material known to the authors to be controversial. A map of Italy, for example, illustrates the incidence of the disease in various provinces, and one is struck by the figure of "46" for the Rome area and a "nil return" for, say, southern Sardinia. But the authors are the first to admit that the chronicity of the disease and the presence of a well-equipped Institute in the capital may have an important bearing on the results.

It is pleasant to read of the prominent role played by British rheumatologists, and on turning the pages one occasionally gets the impression that one is going through a list of the senior members of the Heberden Society. A fitting tribute is paid to the pioneer work of the late Gilbert Scott, it appears that out of some forty names suggested for the disease in the past 100 years, that of Buckley (1935)—"ankylosing spondylitis"—is the one favoured by the authors. Therapy, in general, follows British lines but, as is inevitable in a work of this kind, reference is made to methods untried by the authors, some of which (*e.g.* the injection of Thorium-X and its probable deposition in organs such as the liver) would be rejected by an intelligent patient. One is somehow reminded of the old story about George Bernard Shaw and the lady who consulted him because her dog was misbehaving in the house. G.B.S. advised the lethal chamber. "But are you sure he would use it?" asked the lady.

It has now become customary to append summaries in at least two foreign languages and the authors have supplied them in Italian, French, English, German, and Spanish. Foreign papers have been developing a curious tradition in these summaries. They use impeccable French and German but insist on what may be called dutch-bulb-catalogue English. Thus, "tombant d'accord avec les auteurs suédois . . . qui ont apporté des contributions au sujet . . .", and "darin auch mit den schwedischen Forschern . . . übereinstimmend . . .", becomes in English (quoting the whole sentence)—"The authors, agreeing in this even with the Swedish research workers (Engfeldt *et al.*), who have added recently to the argumentative material, think that at the bottom of the apparent, harsh contrast between the findings of a phlogistic imprint, and respectively, degenerative, by the different workers mentioned above, and hence, the different evolutive phases in or during which the various observations befell." Fortunately, the English summary is no guide to the quality of the contents, and a perusal of the bibliography alone (given at the end of each chapter), suggests that it covers all major contributions to the subject.

DAVID PREISKEL.

Ann. rheum. Dis. (1955), **14**, 444.

NEW YORK RHEUMATISM ASSOCIATION

At the Annual Meeting of the New York Rheumatism Association held on April 12, 1955, at Cornell University, the following officers were elected:

President:	Dr. William H. Kammerer
Vice-President:	Dr. Jack R. Dordick
Secretary-Treasurer:	Dr. Bernard Rogoff
Executive Committee:	Dr. Morris Ziff
	Dr. Rubin Klein
	Dr. Charles M. Plotz

The following papers were given at the clinical meeting:

Use of the Hypospray for Intra-Articular Injection. By MORRIS ZIFF, VINCENT CONTRERAS, and FRANK SCHMID, *Study Group on Rheumatic Diseases, Department of Medicine, New York University College of Medicine.*

A preliminary report on the use of the hypospray jet injector for intra-articular injection is presented. The injector forces a fine jet of the material through the skin and subcutaneous tissues, and now, we believe, through the articular capsule.

Various joints of an unembalmed cadaver were initially injected by the hypospray, using trypan blue. On dissection, the dye was found to be deposited in the joint cavity and to some extent in the periarticular tissues. When diodrast was injected into the joints of patients the periarticular localization of the material was evident.

In other studies with the hypospray, 34·5 and 59·6 per cent. of trypan blue in one instance, and 1·2 and 13·6 per cent. of hydrocortisone in another instance, could be recovered from the knee and elbow, respectively.

Clinical studies were limited to small joints of the hands and wrists of 25 patients with rheumatoid arthritis. One hundred injections were made, 15 mg. hydrocortisone acetate in 0·6 ml. using the smaller joints, and 25 mg. in 1 ml. for the wrist and larger joints. After initial trials with the conventional instrument, a special instrument 18 per cent. more powerful was used; this latter gave major improvement in fifteen of eighteen proximal interphalangeal joints, in five of six metacarpophalangeal joints, and in six of eleven wrist joints.

No serious complications have resulted. Mild pain of seconds to minutes is occasionally reported by some patients, especially with small joints. The hypospray is almost uniformly preferred to needle injection.

Effect of Salicylate in Varying Dosage on Urinary Urate Excretion in Gouty Subjects. By A. B. GUTMAN and T. F. YÜ, *Department of Medicine, Mount Sinai Hospital, and Department of Medicine, Columbia University College of Physicians and Surgeons.*

Salicylates paradoxically cause urate retention in small doses, uricosuria in large doses. Thus the mean effect of 2 g. aspirin/day on the 24-hr urinary urate excretion and serum urate levels was −14·4 and +7·5 per cent. respectively (in seven gouty subjects); whereas, with 5·2 g. aspirin/day it was +37·2 and −23·9 per cent. respectively (in 15 gouty subjects) when given alone, and +85·7 and −40·4 per cent. with concurrent sodium bicarbonate 5 g./day, which is itself not uricosuric. Intermediate doses of aspirin, 3 g./day, had little effect on urine and serum urate in six or nine gouty subjects.

Renal clearance studies showed depression of net urate clearance (C urate) when little salicylate was excreted in the urine (low UV-free salicylate) and marked enhancement when UV-free salicylate was high. A curve relating C urate to UV-free salicylate was discontinuous, implying at least two distinct urate tubular transport mechanisms; one for tubular urate reabsorption, suppressed by high UV-free salicylate, the other (?tubular urate excretion) suppressed by low UV-free salicylate. Sodium bicarbonate increases the UV-free salicylate, and hence suppresses tubular reabsorption of urate as the urinary *p*H rises.

Observations concerning the Mode of Action of the Anti-rheumatic Phenolic Acids. By JOSEPH C. TURNER, *Columbia University College of Physicians and Surgeons.*

After intravenous injection gentisate is excreted rapidly and soon disappears from most organs except the skeletal connective tissues, in which it remains for a considerable time. The *in vitro* binding of gentisate by various proteins demonstrated an attachment to serum albumin in the molar ratios that characterize other cations of similar molecular size. Oxidation products of gentisate (gentisoquinone) can be separated electrophoretically into at least four distinct components. Some of these appear to be firmly bound not only by serum albumin but also by insoluble connective tissue proteins, *e.g.* collagen.

It is suggested that the mode of action of the anti-rheumatic phenols may involve their oxidation *in vivo* to quinones which interact with connective tissue, *i.e.* that there is an analogy with the metabolism of homogentisic acid in the alkaptonuric.

Butazolidin. By WILLIAM B. RAWLS, *Polyclinic Hospital.*

Two hundred patients were given Butazolidin for periods varying from one to 24 months. A total of 2,500 blood counts were done; one every week for the first 3 weeks and every 2 weeks thereafter. Where a reduction of the total white cells or polymorphonuclears occurred, blood counts were continued each week. The maximum dosage used was 400 mg. per day. It was necessary to reduce the dose or to omit the Butazolidin in many instances, and in most cases the count returned to normal in a short time, but when the medication was again given, a reduction of the total white count or polymorphonuclears would again occur. Many patients

would tolerate only 100 or 200 mg. daily and some would not tolerate any. One patient developed a true agranulocytosis although receiving only 300 mg. daily for 3 weeks. Another patient with agranulocytosis came under my care, who had been given 600 mg. of Butazolidin daily. Two patients had mild gastric bleeding: one had a previous history of gastric ulcer, but *x* rays showed this to be completely healed, and there was no history of ulcer in the second. There was sodium retention in some but this was not a troublesome factor. Except for the effect upon the blood count, total white cells, and polymorphonuclear count, the toxicity was not particularly troublesome.

Treatment of Various Rheumatic Conditions with Metacortandracin. By WILLIAM H. KAMMERER and RUSSELL L. CECIL, *New York Hospital.*

Meticorten, or prednisone* is a more potent antirheumatic agent than either cortisone or hydrocortisone.

To date, major side-effects, in a group of 56 patients with rheumatoid arthritis and ten patients with osteoarthritis, have been limited to one patient with peptic ulcer and one with thrombophlebitis. These may or may not have been drug-induced. This report deals only with short-term results. Whether improvement will be maintained under treatment, remains to be seen.

Untoward Reactions to Metacortandracin. By CHARLES M. PLOTZ, *Mount Sinai Hospital Musculo-skeletal Team.*

Metacortandracin has now been widely used in the management of rheumatoid arthritis and related disorders and in allergic conditions. The author has used this new synthetic hormone in thirty such cases with the usual good result in most instances.

Three patients (10 per cent.) of the series developed untoward reactions while on the hormone:

(1) A 61-year-old male developed an area of activity surrounding an old pulmonary cavitation, probably tuberculous.
(2) A 52-year-old female with no previous gastric complaints developed severe abdominal pain of the type associated with active peptic ulcer, terminated only by elimination of the hormone.
(3) A 50-year-old female with mild psoriasis and severe rheumatoid arthritis developed severe generalized psoriasis during treatment.

It is recognized that this high incidence of untoward reactions may be coincidental, particularly in view of the absence of such reactions from other reports. It is further recognized that metacortandracin is of unquestioned value in the management of responsive disorders. This report is tendered to serve as a warning that the hormone is a potent agent capable of producing severe side-reactions and should therefore be used with care.

Preliminary Clinical Trials with Metacortandracin. By J. R. DORDICK, *Beth Israel Hospital.*

Twelve patients with active rheumatoid arthritis previously treated with cortisone, corticotropin, or hydrocortisone were directly transferred to Δ^1-dehydrocortisone (prednisone; Meticorten). Previous results in these patients had been unsatisfactory, or accompanied by undesirable side-effects, or both. During 3 months of observation, it was found that the new steroid (Meticorten) produced a rapid, effective, and consistent anti-inflammatory response on oral administration, exhibiting subjective improvement, as well as objective benefits, reduction in temperature, and sedimentation rate.

Meticorten is four to five times more potent than cortisone or hydrocortisone. Serial studies of the urine or serum electrolytes demonstrated no significant sodium retention or potassium depletion, when therapeutic doses were administered, on a fixed sodium dietary intake. Salt-loading experiments in four cases substantiated this.

The pattern of relapse or recrudescence after abrupt or total withdrawal of Meticorten was similar to that seen after sudden discontinuance of cortisone.

Although cortisone, hydrocortisone, and Meticorten are qualitatively identical in suppressing active rheumatoid arthritis, Meticorten is quantitatively superior and free from serious metabolic, water, or electrolyte disturbances. This is a short-term report, and it is emphasized that the suppressive doses never exceeded 30 mg. per day. The average maintenance dose was 10 to 15 mg. daily.

Treatment of Scleroderma, Sclerodactylia, and Calcinosis by Chelation. By RUBIN KLEIN and SAMUEL B. HARRIS, *Greenpoint Hospital.*

A 45-year-old female had been ill for 11 years with collagen disease. During the last 5 years she had definite evidence of scleroderma, sclerodactylia, and calcinosis. This was confirmed by biopsy, *x* rays, and physical examination. The patient was treated with the sodium salt of ethylene diamine tetra acetic acid 20 per cent. (EDTA), 3 g. being added to 500 ml. 5 per cent. dextrose in water and given by slow intravenous drip. The infusion usually took 3 hrs; the treatment was continued on alternate weeks for 8 weeks, and the patient received a total of 84 g. Complete blood, urine, *x* ray, and biopsy studies were made before, during, and after treatment. The blood calcium fluctuated slightly, and the output of calcium in the urine increased up to 300 per cent. After 12 weeks there was about a 90 per cent. loss of calcium in the left elbow and about 30 per cent. in the fingers of the left hand. There were no changes in the fingers of the right hand. Biopsies of the skin showed a definite improvement in the scleroderma. The patients' daily activity and physical condition also improved. There was no evidence of toxicity during treatment or on follow-up 3 months later.

Severe Rheumatoid Arthritis during Four Years of Induced Hyperadrenalism. By DAVID S. HOWELL, *Columbia University College of Physicians and Surgeons* (see p. 429).

Natural History of Marie-Strümpell Arthritis. By BARUCH S. BLUMBERG, *Columbia University College of Physicians and Surgeons* (see p. 432).

* The generic term recently assigned to Meticorten or Metacortandracin by the Council on Pharmacy of the American Medical Association.

HEBERDEN SOCIETY

Annual General Meeting.—This was held at the Royal College of Surgeons, London, on November 25 and 26, 1955. The following papers were read:

DR. J. SHARP (*Manchester University*): Spondylitis and Heart Disease. A group of patients was encountered who appear to have developed valvular heart lesions, an unusual form of spondylitis, and in some cases a chronic peripheral polyarthritis, after repeated and prolonged attacks of rheumatic fever. A few patients with typical ankylosing spondylitis were found to be suffering from aortic incompetence. The relationship of heart and joint lesions in these patients was discussed.

DR. H. F. WEST (*Sheffield*): $\triangle^{-1}$ Cortisone. An account was given of the structure and nomenclature of the recently discovered cortisone analogues. Their ability to suppress the output of urinary 17-hydroxy-corticosteroids was compared to that of cortisol. The theoretical considerations to be kept in mind in comparing the therapeutic value of $\triangle^{-1}$ cortisone with that of cortisone acetate was emphasized as a prelude to a general discussion on the value of this new steroid.

PROF. J. H. KELLGREN (*Manchester University*): Rheumatoid Arthritis in a Population Sample. An urban population sample in the 55-64 age group was investigated for clinical, radiological, and serological evidence of rheumatoid arthritis. The clinical disease showed the customary four-fold preponderance in females, but the serological and radiological findings did not show this preponderance.

DR. J. S. LAWRENCE (*Manchester*): Osteo-Arthritis in a Population Sample. Radiological studies were undertaken on persons between the ages of 55 and 64 included in the original Leigh survey of rheumatic complaints. The high prevalence of osteo-arthritis and the tendency to multiple joint involvement, particularly in females, was confirmed. The joint pattern in osteo-arthritis was discussed in relation to possible causative factors.

DR. V. WRIGHT (*Stoke Mandeville*): Arthritis and Psoriasis. The clinical manifestations and the results of laboratory tests (D.A.T., measurements of serum proteins, and alkaline phosphatase) in 32 patients with psoriasis and arthritis were analysed. The modifying effect on the picture of erosive arthritis of the association with psoriasis, and the relation of the arthritis to lesions of the skin and nails was discussed.

DR. D. S. JACKSON (*Manchester University*): Isolation and Some Properties of a Neutral Salt-Soluble Collagen. A new method of isolating and purifying the so-called "alkali-soluble collagen" was reported. This involved extration of the skins of young rabbits with neutral salt solutions followed by repeated precipitation with saturated NaCl or $(NH_4)_2SO_4$. Physico-chemical methods suggested that the particle in solution was rod-shaped, the rods aggregating to produce fibrils of 100 Å diameter having a 2,000 Å spacing, which are transformed on warming to 37° C. to fibres of 1,000-2,000 Å diameter and the typical collagen spacing of 640 Å.

DRS. I. C. GILLILAND, I. ISDALE, and E. M. ABD EL WAHAB (*Postgraduate Medical School, London*), introduced by E. G. L. Bywaters: Serum Protein Studies in the Course of Rheumatic Fever. A study of serum proteins in rheumatic fever by electrophoresis on paper confirmed that changes occur in the course of the disease, which may be clinically useful. The consistent changes were a fall in albumin concentration and a rise in 2 globulin concentration, so that the ratios albumin/2 globulin appeared to reflect the course of the disease. A method of obtaining this ratio without detailed fraction analysis was presented.

CORRIGENDUM

In the article by A. M. Lefkowitz and I. J. Farrow in the September, 1955, issue of the *Annals of the Rheumatic Diseases*, on p. 165, col. 1, l. 25, after "fifteen" insert "Stage III".

Ann. rheum. Dis. (1955), **14**, 447.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Biological Studies during the Course of Rheumatic Fever: Collation of Clinical, Haematological, Electrophoretic, and Serological (Antistreptolysin-O) Findings. (Etudes biologiques au cours de la maladie de Bouillaud. Confrontations cliniques, hématologiques, électrophorétiques et sérologiques (antistreptolysine-O) au cours de l'évolution.) CHAPTAL, J., JEAN, R., CAMPO, C., ALRAM, D., and FRAISSE, J. (1954). *Arch. franç. Pédiat.*, **11**, 1055. 3 figs, bibl.

In 39 cases of rheumatic fever admitted to the Clinique des Maladies des Enfants, Montpellier, extensive laboratory investigations were performed throughout the illness, the course of which is described. In fifteen cases the attack was mild and uncomplicated, thirteen patients were more severely ill, with cardiac involvement, and eleven were gravely ill. The treatment consisted in administration of 150 to 200 mg. cortisone daily for 10 to 18 days and of 1,000,000 units penicillin daily. This was followed by intravenous or oral administration of salicylates and in some cases surgical eradication of oral focal sepsis. The blood count showed a neutrophil polymorphonuclear leucocytosis in one-third of the cases, a neutrophilia without leucocytosis in another third, and a normal leucocyte picture in the remaining third. There was no correlation between the gravity of the illness and the blood picture, except that four cases showing a polymorphonuclear leucocytosis had an oral septic focus.

Determination of the serum fibrinogen level gave variable results which were not related to the severity of the disease. The erythrocyte sedimentation rate (E.S.R.) was markedly raised, but the degree of increase was unrelated to the intensity of the illness. Treatment with cortisone reduced its level, but it was usually very slow in returning to normal. No characteristic modification of the electrophoretic pattern of the serum proteins was discernible, either in relation to the disease itself or to its fluctuations. The total albumin content was usually reduced and those of the α, α_2, and γ globulins increased, α_2 globulin taking especially long to revert to normal levels. The appearance of hyperglobulinaemia was taken to indicate a persistent infective focus, but such disturbances of the serum protein pattern as were present during the progress of the illness became normal when the attack was over. Cortisone had the effect of restoring the normal pattern more quickly, but this fact was not helpful in assessing prognosis.

The antistreptolysin titres were commonly raised, though not proportionally to the gravity of the fever, and in some cases they remained normal. The effect of cortisone on these titres was variable, but the performance of tonsillectomy led to a rapid fall in them. Even so, the combination of tonsillectomy, penicillin, salicylates, and cortisone was not necessarily followed by a return to normal titres for many months. In the authors' opinion the occurrence of hyperglobulinaemia suggests some alteration in connective tissue, and this was further confirmed by the finding of an increase in the serum glucoprotein content. Although, on the whole, treatment with penicillin and cortisone was followed by regression of the biological disturbances, as reflected in clinical and biochemical improvement, these drugs are not considered by the authors to have any specific curative effect. *G. W. Csonka.*

Pattern of Hereditary Susceptibility in Rheumatic Fever. WILSON, M. G., and SCHWEITZER, M. (1954). *Circulation (N.Y.)*, **10**, 699. 16 refs.

In a survey carried out at New York Hospital–Cornell Medical Center, the genetical susceptibility to rheumatic fever was studied in 291 families, comprising 646 children, which were under observation for an average period of 10 years. Definite evidence of rheumatic heart disease was required for confirmation of the diagnosis of rheumatic fever in any one individual. The families were selected on the ground that one parent had rheumatic heart disease or was the brother or sister of a patient with known rheumatic heart disease. The distribution of rheumatic fever among the children of these parents was shown to be consistent with the hypothesis that the condition is determined by a recessive gene.

[It is doubtful, however, whether the authors have completely excluded other possible interpretations.]

Harry Harris.

Role of the Streptococcus in the Pathogenesis of Rheumatic Fever. CATANZARO, F. J., STETSON, C. A., MORRIS, A. J., CHAMOVITZ, R., RAMMELKAMP, C. H., STOLZER, B. L., and PERRY, W. D. (1954). *Amer. J. Med.*, **17**, 749. 1 fig., 32 refs.

To determine the relative importance of the Group-A streptococcus in the pathogenesis of rheumatic fever a study was made of young airmen with exudative tonsillitis and pharyngitis admitted to hospital at a U.S. Air Force base in Wyoming. Included in the study were 420 men given 900,000 units procaine penicillin in aluminium monostearate on the 9th, 11th, and 13th days after the onset of illness. 230 men given sulphadiazine, 2 g. on admission and 1 g. every six hours for 5 days, and 220 men who received a placebo and acted as controls. A total of twenty rheumatic episodes occurred between the 10th and 46th days among the sulphadiazine-treated men and the controls, as compared with three episodes among the 420 men who received penicillin on the 9th day after the onset of the illness.

It was concluded that penicillin would prevent rheumatic fever if given 9 days after the onset of illness, but that sulphadiazine was ineffective. Such delay in giving penicillin led to the eradication of streptococci from the nasopharynx, but did not significantly affect the antistreptolysin response. The authors suggest that the development of rheumatic fever requires the presence of living streptococci throughout convalescence from a streptococcal infection.

[The authors' argument is weakened by the fact that five men who received penicillin on the 9th day had already developed rheumatic fever before the drug was given, and three controls and two sulphadiazine-treated subjects had also developed rheumatic fever before the 9th day. It may well be that such cases could be prevented by giving penicillin in the orthodox way—namely, at the beginning of an attack of Group-A streptococcal sore throat.] *R. S. Illingworth.*

Corticotropin and Cortisone in Rheumatic Fever. Preliminary Report of the Effect on the Electrophoretic Patterns of Plasma or Serum Proteins of Children. VAN LEEUWEN, G. J., KELLY, H. G., and JACKSON, R. L. (1955). *Amer. J. Dis. Child.*, **89**, 304. 5 figs, 29 refs.

Since the electrophoretic pattern of the plasma proteins is known to be abnormal in rheumatic fever and to return gradually to normal during recovery, the effect of treatment with corticotrophin (ACTH) or cortisone on the plasma proteins of nine children with rheumatic fever was studied in the hope of elucidating the action of these drugs. In all, 24 specimens of plasma or serum were analysed, blood being taken in all cases on admission and again, if possible, 1½ to 3½ and 5 to 9 weeks later. The findings were compared with those previously obtained in 77 children with rheumatic fever not receiving hormone treatment.

The total protein level was not significantly affected by the treatment. In all but two cases the serum albumin level was decreased before treatment, as was also found in the control group, but in the treated cases the level rose rapidly and reached the normal range in 5 to 9 weeks, compared with an average of 4·2 months in the control group. Similarly the α-globulin level, which was consistently increased in the acute phase, returned to normal more rapidly in the treated group than in the controls, but the fall of the α_2-globulin level, which was similarly increased in the acute phase, was little affected by hormone therapy. The β-globulin level remained elevated or rose during hormone treatment, whereas in the controls it showed no correlation with the activity of the disease. The γ-globulin level fell much more rapidly in patients receiving hormone treatment than in the controls.

It is suggested that these findings support the view "that the major effect of the hormones is related to hypersensitivity processes of the disease" and that they are therefore unlikely to prevent residual cardiac damage.

[It should be noted that the number of patients in this study, and the number of observations made were small.] *C. Bruce Perry.*

Chemoprophylaxis of Acute Rheumatism in Children. (Chemo-prophylaxis van acuut rheuma bij kinderen.) CREVELD, S. VAN, STRONK, M. G., STOPPELMAN, M. R. H., and MAK, G. (1955). *Ned. T. Geneesk.*, **99**, 614. 3 refs.

The authors' main observations made after a 6-year trial (from 1948 to 1954) of sulphadiazine prophylaxis carried out at the out-patient clinic of the Children's Hospital of the University of Amsterdam on 172 out of 246 children with a history of acute rheumatism were:

(1) a delay of 3 months after the acute attack is unnecessary and prophylaxis can be instituted as soon as haemolytic streptococci have disappeared from the throat;
(2) recurrences were more frequent when prophylaxis was irregular or interrupted;
(3) of 2,476 bacteriological examinations of throat swabs only 71 showed the presence of haemolytic streptococci, and four of 49 strains examined were resistant to 8 μg. sulphadiazine per ml. or more;
(4) there were no serious side-effects resulting from prophylactic treatment with sulphadiazine.

It is concluded that the relapse rate in acute rheumatism can be reduced by chemoprophylaxis. *R. Crawford.*

Treatment of Acute Rheumatic Fever in Children. Co-operative Clinical Trial of ACTH, Cortisone, and Aspirin. MEDICAL RESEARCH COUNCIL and AMERICAN HEART ASSOCIATION (1955). *Brit. med. J.*, **1**, 555. 6 figs, 6 refs.

This report gives the detailed results of a large-scale, long-term investigation into the relative efficacy of ACTH (corticotrophin), cortisone, and aspirin in suppressing the manifestations of acute rheumatism and in preventing rheumatic heart disease. Centres on both sides of the Atlantic collaborated in the investigation, which was planned jointly by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.

In all, 497 children under 16 were treated, most of them for a standard period of 6 weeks, and were observed in hospital for a further 3 weeks after the completion of treatment. After discharge, follow-up examinations were made at specified intervals up to one year from the start of treatment. All patients were protected against streptococcal infection with penicillin and sulphadiazine while in hospital, and subsequent throat infections were treated with penicillin. The allocation of patients to the three treatment groups was made at random according to a predetermined order which was unknown to the admitting physician. The diagnostic criteria were laid down as precisely as possible, the major manifestations being carditis, polyarthritis, chorea, subcutaneous nodules, and erythema marginatum; fever, raised erythrocyte sedimentation rate (E.S.R.), evidence of previous streptococcal infection, increased P–R interval, and a reliable history of rheumatic fever or evidence of pre-existing rheumatic heart disease were regarded as minor manifestations. The presence of two major or one major and two minor manifestations were required for diagnosis. The three treatment groups were approximately equal in size and largely similar with regard to the distribution of these manifestations in the two countries, except that nodules were more frequent in Great Britain. [For details of the dosage schedules employed, the reader should consult the original paper.]

The effects of treatment on the temperature and pulse rate were roughly the same in all three groups, though in those treated with hormones the pulse rate showed some tendency to rise during the sixth to ninth weeks. The E.S.R. fell more rapidly with hormone treatment, but by the thirteenth week it had reached the same level in all groups. No differences were discovered in the effect on joint involvement, chorea, and erythema marginatum. New nodules appeared during treatment in all groups, but persisted longer in the group receiving aspirin.

There was a tendency for patients treated with ACTH or cortisone to show a temporary increase in heart size, but the P–R interval, when prolonged, showed a more rapid initial decrease in these groups. The development of cardiac murmurs bore no relation to treatment. The disappearance of soft apical systolic and mid-diastolic murmurs was more rapid with hormone treatment, but there were no differences in their incidence at the end of a year. The appearance and disappearance of loud apical systolic and basal diastolic murmurs were unrelated to therapy and at the end of a year there was no difference between the groups in respect of this type of murmur. The occurrence and course of pericarditis were similarly unaffected by the type of treatment received, which similarly had no appreciable effect on the course of the disease in seriously ill patients with congestive heart failure.

Most of the patients receiving the hormones, but relatively few of those receiving aspirin, developed side-effects. Only six deaths occurred among the 497 patients.

It is concluded that there was no evidence to suggest that rheumatic fever in children can be uniformly arrested by any of the three agents used or that there is any significant difference between them in their effect on the cardiac status of the patient at the end of one year.

[This model investigation has produced a wealth of data to which no abstract can do justice.] *G. Loewi.*

Causes of Death in Rheumatic Heart Disease. Relationship to the Incidence of Mitral Stenosis occurring Alone or with Other Valvular Lesions. SOLOFF, L. A., and ZATUCHNI, J. (1955). *Amer. J. Med.*, **18**, 419. 10 refs.

The causes of death in 141 cases at Temple University and Episcopal Hospitals, Philadelphia, in which rheumatic heart disease was diagnosed clinically were analysed, with special reference to the incidence of mitral stenosis. The causes of death were heart failure (39·7 per cent., acute carditis (13·5 per cent.), bacterial endocarditis (11·3 per cent.), systemic embolism with pre-existing heart failure (9·2 per cent.), systemic embolism without failure (8·5 per cent.), and pulmonary infarction (6·4 per cent.). In the remainder, death was not related to rheumatic heart disease or its sequelae. The authors point out that an analysis based on deaths only is a form of selection, since "it is the persons who die earliest—that is, the poorest risks—who are used to determine prognosis figures". Mitral stenosis in combination with other valvular lesions was about twice as common as isolated mitral stenosis. A clinical diagnosis of isolated mitral-valve disease was made in 49·7 per cent. of the cases, but was confirmed at necropsy in only 26·1 per cent., this error in the clinical diagnosis being most frequent in patients who died from congestive failure. Calcification of the mitral valve was found at necropsy in 13 per cent. of cases, but not as an isolated valvular lesion. *James W. Brown.*

Focal Pulmonary Hemosiderosis in Rheumatic Heart Disease. ESPOSITO, M. J. (1955). *Amer. J. Roentgenol.*, **73**, 351. 14 figs, 27 refs.

It is pointed out that focal pulmonary haemosiderosis is not so rare a sequel of rheumatic heart disease as some reports appear to indicate. At the New York Hospital–Cornell Medical Center examination of lung sections obtained at necropsy in 100 selected cases of rheumatic heart disease revealed 28 cases of focal haemosiderosis. Other findings at necropsy were mitral stenosis in 24 cases and aortic narrowing in four. The incidence of haemoptysis was high, but there were no other distinctive clinical features. *J. B. Enticknap.*

Mucoproteins in Rheumatic Fever in Infancy. (Le mucoproteine nella malattia reumatica dell'infanzia.) FANTUZZI, B., and NEUHAUS, C. (1955). *Minerva pediat.* (*Torino*), **7**, 478. 3 figs, 27 refs.

At the Paediatric Clinic, University of Milan, the authors determined the serum mucoprotein level in eight normal children and in thirteen suffering from rheumatic fever. They found that in the latter group the increased values for the serum mucoprotein content during the febrile period corresponded more closely to the clinical course of the illness than did the erythrocyte sedimentation rate, and thus this determination may be of value in diagnosis and prognosis. *L. Michaelis.*

Follow-up Studies in Rheumatic Fever Patients. A Preliminary Report. BIORCK, G., and HALL, P. (1955). *Acta rheum. scand.*, **1**, 119.

Rheumatic Restenosis of Mitral Valve. Report of a Case with Death almost 5 Years after Mitral Valvulotomy. MCKUSICK, V. A. (1955). *Arch. intern. Med.*, **95**, 557. 3 figs, 8 refs.

Aetiology of Acute Articular Rheumatism. (Zur Ätiologie des akuten Gelenkrheumatismus.) WEITZ, W. (1955). *Dtsch. med. Wschr.*, **80**, 617. 3 figs, 5 refs.

Acute Rheumatism in Childhood. (Le rhumatisme aigu chez l'enfant.) DUBOIS, R. (1954). *Acta physiother. rheum. belg.*, **9**, 179.

Ballistocardiographic Study of Body Acceleration during the Acute and Convalescent Stages of Rheumatic Fever. ARBEIT, S. R., DOLAN, M. A., and STOLLERMAN, G. H. (1955). *Amer. Heart J.*, **49**, 647. 4 figs, 9 refs.

Effect of Salicylates on the Vitamin C Stores of Rheumatic Fever Patients. ALBANESE, A. A., HIGGONS, R. A., AVERY, W. G., and DILALLO, R. (1955). *N.Y. St. J. Med.*, **55**, 1167. 5 refs.

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

Joint Fluid Changes in Rheumatoid Arthritis. ROBINSON, W. D., DUFF, I. F., and SMITH, E. M. (1955). *J. Mich. med. Soc.*, **54**, 270. 8 figs, 22 refs.

After a discussion of the characteristics of synovial fluid the authors describe a study carried out at the University of Michigan, Ann Arbor, of the changes in the joint fluid in rheumatoid arthritis following the systemic administration of cortisone and ACTH (corticotrophin) and also the intra-articular injection of hydrocortisone. Cell counts were made, the quality of the mucin clot formed on addition of acetic acid was observed, the relative viscosity was determined by means of an Ostwald viscosity pipette, and the polysaccharide concentration in the fluid was estimated by the method of Ragan and Meyers (*J. clin. Invest.*, 1949, **28**, 56; *Abstracts of World Medicine*, 1949, **6**, 351), with certain modifications. The authors confirmed a finding of Ragan and Meyers that there is a linear relationship between the concentration of polysaccharide in the synovial fluid and the logarithm of the viscosity of the fluid. Since the concentration of polysaccharide in rheumatoid joint fluid is not greatly altered from that of normal fluid, whereas the viscosity is distinctly lowered, it has been suggested that the polysaccharide in the fluid is poorly polymerized. The ratio of log. viscosity to polysaccharide concentration (the "polymerization index") is therefore considered to give a rough indication of the degree of polymerization of the polysaccharide in joint fluid.

In a number of patients with long-standing rheumatoid arthritis receiving ACTH, cortisone, or hydrocortisone systematically in high dosage the following changes in the joint fluid were observed:

(1) a reduction in the cell count, especially affecting the polymorphonuclear leucocytes;
(2) a change in the quality of the mucin clot in the direction of normal;
(3) an increase in viscosity; and
(4) an increase in the so-called "polymerization index".

These effects were not observed when cortisone or hydrocortisone was given in doses under 100 mg. daily, and not in all cases receiving higher doses. The improvement in the characteristics of the joint fluid was rarely maintained with prolonged treatment. The same beneficial effects were noted in the fluid from 35 joints of patients receiving serial intra-articular injections of hydrocortisone. In a discussion of the use of intra-articular hydrocortisone in the treatment of rheumatoid arthritis the authors conclude that it may be of great value in selected cases. *C. E. Quin.*

Treatment of Rheumatoid Arthritis by Prolonged Stimulation of the Adrenal Cortex. WEST, H. F., and NEWNS, G. R. (1955). *Lancet*, **1**, 578. 4 refs.

The results of long-term treatment with corticotrophin, at the United Sheffield Hospitals, of eleven cases of rheumatoid arthritis are described and compared with those of a previously reported (*Lancet*, 1953, **2**, 1123; *Abstracts of World Medicine*, 1954, **15**, 334) investigation in which cortisone was used. In all eleven cases the disease was active and progressive and no improvement had been obtained with conservative treatment. The series consisted of six males aged 16 to 51 and five females aged 46 to 69. Treatment was maintained for from 12 to 24 months and is still being continued. The dosage of corticotrophin varied from 7½ to 40 units daily by intramuscular injection and was adjusted to produce a daily urinary output of 15 to 40 mg. 17-ketogenic steroids. The only complications noted were pigmentation in two cases and a rise in diastolic blood pressure in four cases.

Comparison with the earlier series treated with cortisone acetate leads the authors to conclude that controlled administration of corticotrophin has produced better results so far. In particular, only two of the patients treated with corticotrophin showed any increase in bony erosion, whereas this occurred in seventeen of the 27 cases treated with cortisone. Disadvantages of the treatment are said to be the need for daily injections (though these can be self-administered) and for frequent urinary assays. *Kathleen M. Lawther.*

Amyloidosis in Rheumatoid Arthritis, and Significance of "Unexplained" Albuminuria. A Report of Eight Cases. FEARNLEY, G. R., and LACKNER, R. (1955). *Brit. med. J.*, **1**, 1129. 4 figs, 5 refs.

Cases of rheumatoid arthritis associated with amyloid disease are seen from time to time, but there is little information about the frequency of this serious complication. With this in mind the authors studied all the cases of rheumatoid arthritis seen by them in one

year at the Postgraduate Medical School of London. These, numbering 183, were examined for the presence of albuminuria, regarded as being the most useful clinical pointer to possible amyloidosis. Persistent albuminuria was found in 24 cases, being without explanation in twelve. Of these twelve patients one died at an emergency operation, and in four investigation was impossible. The remaining seven cases were investigated by Unger's modified Congo-red test or liver biopsy or by both methods, a positive result being obtained in all seven. Extensive amyloidosis was also found at necropsy in the fatal case referred to above.

That eight cases were discovered among 183 patients with rheumatoid arthritis suggests that amyloidosis is not a rare complication of this condition. The duration of the arthritis in these eight cases ranged from one to 18 years, but in six of the eight patients it has been present for more than 10 years. Only one patient had clinical enlargement of both liver and spleen; four had hepatomegaly alone and three splenomegaly alone.

K. C. Robinson.

Gold-Hormonal Therapy in Rheumatoid Arthritis. BILKA, P. J., and WEIL, M. H. (1955). *Ann. intern. Med.*, **42**, 638. 13 refs.

The aim of the investigation reported here from the University of Minnesota Medical School, Minneapolis, was to determine whether treatment with gold and cortisone combined was more effective than with either agent alone in rheumatoid arthritis. A series of 41 patients were given a minimum total dose of 500 mg. aurothioglucose in combination with cortisone or corticotrophin therapy and were followed up for at least 3 months after cessation of hormone treatment. In 17 per cent. there was a complete remission, in 39 per cent. major improvement, and in 12 per cent. moderate improvement, the rest showing no change. These results are stated to approximate those obtained with gold alone. There were side-reactions to gold in 46 per cent. of cases. It is concluded that combined therapy has little to recommend it.

[From the data supplied and in the absence of any controls, it is impossible to judge the validity of the authors' conclusions.] *G. Loewi.*

Diagnosis of Rheumatoid Arthritis. (El diagnostico de la artritis reumatoide.) SVARTZ, N. (1955). *Rev. clin. esp.*, **56**, 226. 2 figs.

Rheumatism resembling Rheumatoid Arthritis. WEISS, T. E. (1955). *J. Louisiana med. Soc.*, **107**, 147. 13 refs.

Rheumatoid Disease of the Lungs and Pleura. SPENCE, M. P. (1955). *Arch. Middx Hosp.*, **5**, 95. 6 figs, 21 refs.

Rheumatoid Arthritis and Arterial Pressure. JARVINEN, K. A. J. (1955). *Acta rheum. scand.*, **1**, 127. 2 figs, 9 refs.

Hemagglutination Test for Rheumatoid Arthritis. IV. Characterization of the Rheumatoid Agglutinating Factors by Analysis of Serum Fractions prepared by Ethanol Fractionation. HELLER, G., KOLODNY, M. H., LEPOW, I. H., JACOBSON, A. S., RIVERA, M. E., and MARKS, G. H. (1955). *J. Immunol.*, **74**, 340. 18 refs.

Rheumatoid form of Infantile Leukaemia. (La forma reumatoide della leucemia infantile.) FORNARA, P. (1955). *Med. internaz.*, **63**, 81. 4 figs.

Bufferin in the Management of Rheumatoid Arthritis. FREMONT-SMITH, P. (1955). *J. Amer. med. Ass.*, **158**, 386. 8 refs.

Electromyographic Study of the Atrophied First Dorsal Interosseus Muscle in Rheumatic Arthritis. [In English.] PETERSÉN, I. (1955). *Acta rheum. scand.*, **1**, 67. 1 fig., 23 refs.

Occurrence of Amyloid in Rheumatoid Arthritis. Some Observations. [In English.] LAINE, V., VAINIO, K., and RITAMA, V. V. (1955). *Acta rheum. scand.*, **1**, 43. 1 ref.

Rheumatoid Arthritis aggravated by Pregnancy and controlled by Cortisone. GOULD, I. D. (1955). *N.Y. St. J. Med.*, **55**, 1164. 1 ref.

(Osteo-Arthritis)

Techniques for the Intra-Articular Injection of Hydrocortisone into the Hip-Joint. The Direct Anterior Approach. (Des techniques d'injections intra-articulaires d'hydrocortisone dans la hanche. La voie antérieure a "l'aplomb".) LEBON, J., BACRI, J., and AMOUYAL, J. (1955). *Sem. Hôp. Paris*, **31**, 1669. 5 figs.

Treatment of Osteo-Arthritis of the Knee Joint. ROSE, G. K. (1955). *Rheumatism*, **11**, 36. 1 fig., 10 refs.

Prophylaxis of Degenerative Joint Diseases. (Prophylaxe der degenerativen Gelenkerkrankungen.) FÄHNDRICH, W. H. (1955). *Z. Rheumaforsch.*, **14**, 107.

(Spondylitis)

Psoriasis Spondylitica. FLETCHER, E., and ROSE, F. C. (1955). *Lancet*, **1**, 695. 12 refs.

Among 100 consecutive cases of ankylosing spondylitis treated at the Royal Free Hospital, London, four cases were found in which psoriasis was also present. In view of the fact that the incidence of psoriasis in the general population is about 0·3 per cent., the authors regard this finding as indicating the existence of an association between ankylosing spondylitis and psoriasis comparable to that known to exist between rheumatoid arthritis and psoriasis. The four cases are described in detail. Psoriasis developed before the ankylosing spondylitis in

all of them. The spondylitis was clinically indistinguishable from the disease as it occurs without psoriasis. There was a family history of ankylosing spondylitis or psoriasis in two cases, one patient having four relatives with ankylosing spondylitis but none with psoriasis; the other four had relatives suffering from psoriasis, but none from spondylitis. In view of reports that ulnar deviation and iritis do not occur in psoriasis arthropathica, it is of interest that one of the patients in the present series, who suffered from psoriasis and spondylitis with involvement of the peripheral joints, has both these complications.

The authors suggest that, by analogy with psoriasis arthropathica, the combination should be called psoriasis spondylitica. *C. E. Quin.*

Effect of Ankylosing Spondylitis on Ventilatory Function. ROGAN, M. C., NEEDHAM, C. D., and MCDONALD, I. (1955). *Clin. Sci.*, **14**, 91. 8 refs.

The ventilatory function of 35 patients of both sexes, ranging in age from 20 to 60 and suffering from ankylosing spondylitis but without cardio-pulmonary disease, was studied at Aberdeen Royal Infirmary before, during, and in 22 cases up to 18 months after, treatment by radiotherapy. Before treatment most of the patients showed low vital capacity and total lung volume, presumably due to the restricted movement of the chest, and the residual volume therefore constituted an abnormally high proportion of the total lung volume. This, however, did not signify the presence of emphysema, as was confirmed by the finding of a normal mixing efficiency. The maximum breathing capacity was not reduced in proportion to the vital capacity, presumably because these subjects have unusually free diaphragmatic movements and may thus achieve maximum breathing capacity by breathing at a more rapid rate than normal, though this was not measured on these subjects.

After radiotherapy there was no significant increase in total lung volume, but vital capacity and timed vital capacity increased, and residual volume decreased. The other indices of lung function all showed improvement, although the changes were not statistically significant for all tests. (There was no control group as the authors did not feel it was justifiable to withhold radiotherapy from any of these patients.) *W. A. Briscoe.*

Spondylitis Ankylopoietica. (A Contribution to its Definition and Etiology.) [In English.] DRUCKMANN, A., and FRÄNKEL, M. (1955). *Acta med. orient.* (*Tel-Aviv*), **14**, 33. 10 figs, 46 refs.

(Miscellaneous)

Radiotherapy of Chronic Arthritis, Spondylitis, Humeroscapular Periarthritis, and Epicondylitis. (Die Röntgentherapie der Arthrosen, Spondylosen, der Periarthritis humeroscapularis und der Epikondylitis.) HESS, P., and BONMANN, K. H. (1955). *Strahlentherapie*, **96**, 75. 18 refs.

At Bethesda Hospital, Duisburg, Germany, 664 cases of "arthritis deformans", including some spinal cases, were treated by *x* rays, two doses of 100 to 200 r being given at 3 days' intervals, and repeated once or twice after 6 to 12 weeks. The results showed that 12·6 per cent. of the patients were symptom-free, 43·8 per cent. improved, and 43·5 per cent. derived no benefit. As these results were inferior to most of those reported in the literature, a closer investigation was therefore made, including a follow-up examination 6 months or more later. This showed a significant tendency to relapse although, conversely, improvement in some cases was delayed. In 364 cases followed up there was early or late improvement in 86 per cent., a figure in general agreement with other published results. However, when the after-history was taken into account, this figure fell to 60 per cent., and 14 per cent. remained completely refractory. In the authors' view, lack of adequate follow-up appears to be responsible for the misleading impression given in most published series.

In humero-scapular periarthritis (now generally attributed to osteosclerosis of the cervical spine), treatment by radiation in 110 cases failed in only 13·8 per cent. In 56 cases of epicondylitis (at the tendon insertions of the elbow), radiation treatment was unsuccessful in only 10 per cent. The authors conclude that *x*-irradiation is the best treatment for all cases of this type. *J. Walter.*

Contribution to the Radiotherapy of Arthritis of the Knee Joint. (Beitrag zur Röntgentherapie der Kniegelenkarthrosen.) KRAUTZUN, K., and ELINGSHAUSEN, H. P. (1955). *Strahlentherapie*, **96**, 82. 9 refs.

The authors point out that it is significant that there has recently been a tendency in irradiation therapy of arthritic knee-joints to decrease the dose, without apparently impairing results. In most cases symptoms are certainly not related to the degree of radiological change in the joint and are probably mainly dependent on secondary vascular effects. It seems reasonable, therefore, the authors suggest, to use methods that have proved valuable in leg ulcers, Raynaud's gangrene, scleroderma, and similar conditions, in which treatment has been directed to the autonomic nervous system, particularly as in more recent theories of aetiology vertebral osteochondrosis and Selye's adaptation syndrome have been mentioned.

On this basis, since 1946 all cases of arthrosis of the knee-joint have been treated at Knappschafts Hospital, Bottrop, Germany, by deep *x*-ray therapy directed in the first instance to the knee-joint itself. If this failed, the thoraco-lumbar sympathetic chains were irradiated by a spinal field on each side, 15 × 10 cm. in size, directed medially at 60°, 150 to 200 r being given on each field. In climacteric cases in women, the pituitary region was sometimes also included, 100 r being given to each of two lateral fields, 15 × 10 or 10 × 8 cm. in area. Local treatment alone failed in 15 per cent. of cases; but of these non-responding cases, treated by the above techniques, 40 per cent. were rendered symptom-free or much improved, 35 per cent. improved, and 25 per cent. remained unchanged. *J. Walter.*

Focal Paget's Disease of the Skull (Osteoporosis Circumscripta). COLLINS, D. H., and WINN, J. M. (1955). *J. Path. Bact.*, **69**, 1. 13 figs, 15 refs.

Since its original description as a radiological entity by Schüller (*Brit. J. Radiol.*, 1926, **31**, 156) osteoporosis circumscripta has been widely recognized as a form of focal rarefaction of the flat bones of the skull occurring in adults. In many instances the skull lesion appears to be an isolated one, but a number of cases have been recorded where indubitable lesions of Paget's disease of bone were present or were found to develop in other parts of the skeleton. The view is thus generally held that the condition is a manifestation of Paget's disease. A few pathological reports of isolated cases, including those of Sosman (*Radiology*, 1927, **9**, 396) and of Erdheim (*Beitr. path. Anat.*, 1935-6, **46**, 1), have described histological changes similar to those seen in Paget's disease, but until now little pathological evidence regarding the nature of the condition has been available.

In the present paper are described five cases of osteoporosis circumscripta discovered in a careful survey of calvaria removed during necropsy at the General Infirmary at Leeds. This corresponds to an incidence of one in 350 to 400 necropsies; thus the condition is much less common than the usual form of Paget's disease. The ages of the five patients concerned—four men and one woman—were respectively 43, 57, 61, 78, 80 years. One case showed changes of Paget's disease in the bones of the pelvis.

In each of the five cases the histological characteristics of the skull lesions were those of Paget's disease of bone. Occasional thickened trabeculae showed the characteristic mosaic of cement lines separating areas of bone with disoriented lamellar structure, but the bulk of the abnormal tissue consisted of slender, newly formed bone trabeculae, conspicuous vascular spaces, and fibrous tissue. Bone resorption greatly exceeded new bone formation.

The authors accept the view that the initial lesion of Paget's disease is bone destruction. Because simple osteoporosis of senile type involved the vertebrae in three of the five cases they tentatively suggest that in osteoporosis circumscripta the failure of the productive phase that generally follows in Paget's disease may be associated with the same influences that impair osteoblastic activity in senile osteoporosis. *H. A. Sissons.*

The Old Arthritic Family. (La vieille famille arthritique.) GIRAUD, G. (1954). *Montpellier méd.*, **46**, 591.

The term "arthritis" has remained in general use in spite of attempts to replace it by more exact definitions. Similarly, "the arthritic family" is a concept well known to clinicians, both ancient and modern. The arthritic "soil" or constitutional predisposition may consist of several components, but some discrimination is here necessary. Thus, simple obesity may be included, but not the glandular types; similarly, a hyperglycaemic tendency may be a significant feature of the arthritic diathesis, but not diabetes in young subjects, or progressive or unstable diabetes. In those possessing the required constitution, the precipitation from the blood of certain substances will give characteristic results. Gout is an example of such a condition, the sufferer being handicapped by his endogenous hyperuricaemia, though the precipitate consists not only of urates, but also of cholesterol and oxalates; deformities of the joints and the growth of tophi follow in due course. Nephrolithiasis has been called "the brother of gout", in that somewhat similar constitutional factors are present although the clinical expression is directed towards a different system. Cholesterol precipitation results in gall-stones, xanthomata, and xanthelasma, and analogous processes are probably at work in the formation of salivary and pancreatic calculi and arterial atheroma.

It is possible, therefore, that a similar type of acute reaction to the precipitation of some metabolite may account for those chronic and degenerative forms of rheumatism to which the term "arthritic diathesis" is empirically applied, and the symptomatology of which includes the presence of peri and intra-articular "deposits" and of "nodes" with accompanying tissue reactions. The characteristic sudden bursts of transient activity suggest an unstable and absorbable precipitate. It is here, possibly, that allergy and "stress" play their part.

David Preiskel.

Value of Phenylbutazone in the Treatment of Rheumatoid Arthritis as determined by Clinical Response and by the Serum Protein/Polysaccharide Ratio (PR). PAYNE, R. W., SHETLAR, M. R., FARR, C. H., HELLBAUM, A. A., and ISHMAEL, W. K. (1955). *J. Lab. clin. Med.*, **45**, 331. 13 refs.

The use of phenylbutazone ("Butazolidin") in the treatment of rheumatic disorders has tended to be discredited because the drug appears to have little influence on the erythrocyte sedimentation rate (E.S.R.) and the incidence of toxic reactions is high. Since the serum protein/polysaccharide ratio (PR) has been shown to reflect the degree of rheumatoid activity, it may be of objective value in assessing the results of therapeutic measures in rheumatic conditions. The authors, from the University of Oklahoma School of Medicine, report the results of a placebo-controlled investigation of the comparative effects of phenylbutazone and cortisone on the PR in 61 patients suffering from various rheumatic diseases.

In patients with rheumatoid arthritis, during the active stage of which the PR is high, a significant and comparable fall in the PR was obtained with a fractionated daily dosage of 200 to 600 mg. phenylbutazone or 100 to 200 mg. cortisone. Similarly, in three patients with active ankylosing spondylitis, one with acute lupus erythematosus, and one with tophaceous gouty arthritis, administration of phenylbutazone resulted in a reduction in the PR; when the drug was withdrawn there was a prompt exacerbation of clinical rheumatoid activity and a rise in the PR. The E.S.R. was of little aid, reflecting only very gross changes in the disease state. Toxic effects, mainly anaemia, a skin rash, and gastro-intestinal disturbances, were observed in 14 per cent. of the patients

given phenylbutazone, but none of these reactions persisted after the drug was discontinued.

[The authors' conclusion that phenylbutazone can be prescribed with "a reasonable factor of safety" does not reflect the present general view in Britain.] *P. I. Reed.*

Enlargement Radiography of the Petrous Bone in Osteitis Deformans (Paget's Disease). (La radiographie agrandie du rocher dans l'ostéite déformante de Paget.) JUSTER, M., MICHEL, J., FISCHGOLD, H., and LIÈVRE, J. A. (1955). *Presse méd.*, **63**, 308. 8 figs, 7 refs.

After preliminary studies in which sections of dried temporal bone varying in thickness from 1 to 10 mm. were examined with the radiographic enlargement technique using a fine focus tube of 0·3 mm. in diameter which gave a magnification of × 2 to × 2·2, the technique was then applied to examination of the petrous bone in 24 confirmed cases of Paget's disease. The method, which was fully described by Layani and Fischgold (*Presse méd.*, 1953, **61**, 279) gives considerable additional information over unenlarged radiographs.

In the petrous bones examined there was progressive resorption of the cortex and compact bone surrounding the labyrinth and internal auditory canal, and at the tip of the petrous the compact bone was separated by cracks which in some cases enlarged into cavities. In only three out of the 24 specimens examined were the petrous bones normal; in the others the following lesions were observed:

(1) Damage to the cortex of the superior border varying from a simple thinning to complete disappearance.
(2) Damage to the cancellous bone, consisting in a reduction in the thickness and number of the trabeculations; in one case, however, there was increased density of the petrous.
(3) An increased visibility of the internal auditory organs; in the case with increased density of the petrous, however, these organs were less visible than usual.
(4) Disappearance to a greater or less extent of the dense bone surrounding the internal ear was seen in fourteen cases, in some being confined to either the cochlea or the labyrinth. In more than half the cases the changes were bilateral and symmetrical.

There appeared to be no direct relation between the extracranial changes and those in the petrous bone, but there was a close relationship between the other changes in the skull and those in the petrous. While changes in the petrous bone were always present when there were significant changes in other parts of the skull, in three cases the petrous changes were the only ones present. Of the 24 patients, fifteen had deafness of some degree, the degree of deafness being directly correlated with the radiological changes, so that those cases with the most marked radiological changes showed the most severe changes in the internal ear.

John H. L. Conway-Hughes.

Ocular Changes in Acute Systemic Lupus Erythematosus. CLIFTON, F., and GREER, C. H. (1955). *Brit. J. Ophthal.*, **39**, 1. 4 figs, 16 refs.

According to the authors the only report in the British literature of the histological examination of the eye in acute systemic lupus erythematosus is that of Semon and Wolff (*Proc. roy. Soc. Med.*, 1933, **27**, 153), who found only mild choroiditis and subretinal exudation. In the present paper the clinical, ophthalmological, and pathological findings in two further cases seen at Bristol hospitals, both of which terminated fatally, are described. On general examination no new or unusual features were seen, but a notable finding on histological examination of the eye was the presence of cytoid bodies in the nerve fibre layers of the retina, particularly at the posterior pole and around the disk. The rods and cones near the disk had undergone granular degeneration, inducing a shallow retinal detachment. Differing views on the nature and origin of cytoid bodies and the conditions in which they occur are discussed. The authors suggest that cytoid bodies are exudates in the nerve fibre layer resulting from damage to the capillary endothelium which permits the escape of plasma and erythrocytes.

F. D. McAuley.

Reiter's Disease. A Review of the Present Position. BUCHAN, J. F. (1955). *Proc. roy. Soc. Med.*, **48**, 432. 6 tables, 12 refs.

The aetiology remains unknown although it may be due to a strain of the pleuropneumonia group of organisms. It follows abacterial and gonococcal urethritis in men and dysentery in both sexes. The arthritis generally predominates over the urethritis and conjunctivitis. It is self-limiting and resistant to treatment.

P. D. Trevor-Roper.

Lupus Erythematosus Disseminatus. Clinical Features and Prognosis. [In English.] LEIKOLA, E., and VARTIA, K. O. (1955). *Acta rheum. scand.*, **1**, 73. 2 figs, 28 refs.

Aplastic Anaemia following Mepacrine Treatment of Lupus Erythematosus. PATON, M. D., RIDDELL, M. J., and STRONG, J. A. (1955). *Lancet*, **1**, 281. 11 refs.

Apparent Hepatic Dysfunction in Lupus Erythematosus. KOFMAN, S., JOHNSON, G. C., and ZIMMERMAN, H. J. (1955). *Arch. intern. Med.*, **95**, 669. 4 figs, 43 refs.

Inflammatory Rheumatism and Collagen Diseases. (Rhumatismes inflammatoires et collagénoses.) MICHOTTE, L. (1954). *Acta physiother. rheum. belg.*, **9**, 196.

Shoulder–Hand Syndrome. (La sindrome spalla-mano.) ROBECCHI, A. (1955). *Reumatismo*, **7**, 153. Bibl.

Surgical Treatment of Rheumatic Tenosynovitis. HOWARD, L. D. (1955). *Amer. J. Surg.*, **89**, 1163. 5 figs, 12 refs.

Circulatory Disorders in Sudeck's Syndrome. (Durchblutungsstörungen beim Sudeck-syndrom.) BLUMENSAAT, C. (1955). *Z. Rheumaforsch.*, **14**, 94. Bibl.

Radiological Aspects of the Osteo-Articular Changes in the Collagen Diseases. (Aspetti radiologici delle alterazioni osteoarticolari nelle mesenchimopatie reattive diffuse (malattie del collageno).) COSTA, F., and PAPAGNI, L. (1955). *Reumatismo*, **7**, 180. 19 figs, bibl.

Personal Experience in the Treatment of Joint Diseases with Hydrocortisone Acetate (Compound F). (La nostra esperienza nel trattamento di artropatie con l'acetato di idrocortisone (composto F).) GALLI, G., and DAVALLI, C. (1955). *Reumatismo*, **7**, 193. 1 fig., bibl.

Chronic Post-Traumatic Rheumatic Polyarthritis. (Polyarthrite rhumatismale chronique post-traumatique.) ISEMEIN, L., and PADOVANI, J. (1955). *Rev. Rhum.*, **22**, 206.

Disk Syndrome

Low Back Pain treated by Manipulation. A Controlled Series. COYER, A. B., and CURWEN, I. H. M. (1955). *Brit. med. J.*, **1**, 705. 6 refs.

A controlled investigation into the value of manipulation in the treatment of low back pain is reported. A total of 152 patients at St. Thomas's Hospital, London, were divided into two groups without selection, one group being treated by manipulation of the lumbar spine by the method of Cyriax, and the other (control) group by rest in bed and administration of analgesics. No fewer than sixteen of the 76 control patients defaulted.

The authors found that 38 of the 76 patients given manipulation were free from signs and symptoms at the end of a week, whereas only sixteen of the control group were free from pain and disability at this time. At the end of 6 weeks nine in the former group still had signs and symptoms, compared with seventeen in the latter. The authors consider their findings to indicate that manipulation is a logical method of treatment of the patient suffering from low back pain.

[This paper has aroused much interest and controversy. The fact that sixteen out of 76 patients in the control group defaulted has led some observers to question the validity of the authors' results.] *W. Tegner.*

Lumbar Disk Protrusion as a Surgical Emergency. FAIRBURN, D., and STEWART, J. M. (1955). *Lancet*, **2**, 319. 1 fig., 12 refs.

Vertebral Lumbago. (Die vertebrale Lumbalgie.) COP, D. (1955). *Z. Rheumaforsch.*, **14**, 102. 5 refs.

Hydrophilic Properties of the Nucleus Pulposus of the Intervertebral Disk. NAYLOR, A., and HORTON, W. G. (1955). *Rheumatism*, **11**, 32. 18 refs.

Accidents due to Structural Deterioration of the Intervertebral Disk. (Les accidents de la détérioration structural du disque.) SÈZE, S. DE (1955). *Sem. Hop., Paris*, **31**, 2267. 29 figs.

Pain-Relieving Attitudes in the Common Type of Sciatica due to Herniation of the Intervertebral Disk. (Les attitudes antalgiques dans la sciatique disco-radiculaire commune.) SÈZE, S. DE (1955). *Sem. Hôp., Paris*, **31**, 2291. 40 figs.

Gout

Polycyclic Continuous Acute Gouty Arthritis. Long-term Clinical and Metabolic Study. WOLFSON, W. Q. (1955). *J. Mich. med. Soc.*, **54**, 323. 2 figs, 4 refs.

The author describes the clinical and biochemical findings in a case of gout of unusual severity first seen in 1946 and kept under investigation at Wayne University College of Medicine, Detroit. The patient, a man aged 39 years, suffered from frequent attacks of acute gout, marked by intervening periods of only lessened intensity of the symptoms instead of the usual asymptomatic intervals. The case presented special difficulty because the patient was hypersensitive to colchicine. In addition, there was at first a poor response to ACTH (corticotrophin) therapy, but this improved as treatment with this drug was continued. The urinary output of 17-ketosteroids was extremely low. The thyrotrophic, growth, and gonadotrophic functions of the pituitary gland appeared to be normal.

The slow appearance of increased adrenocortical function in spite of persistent stimulation with ACTH suggested the presence of selective hypopituitarism with respect to corticotrophin. This, it was thought, would explain the severity of the gout, since previous investigations have shown that increased endogenous secretion of corticotrophin will ultimately terminate severe attacks of gout. In the early stages of treatment it was found that no more than 0·36 mg. colchicine daily could be tolerated without the development of toxic symptoms. Later, however, it was discovered that 0·42 mg. colchicine daily could be given intravenously and this produced an appreciable reduction in the severity of the symptoms. The hypersensitivity to colchicine was abolished by ACTH therapy when this became available. Thereafter the combination of ACTH therapy with continuous colchicine administration in the maximum tolerated dosage enabled the acute manifestations of gout to be brought under control. Later the serum urate level was restored to normal with probenecid in a dose of 2 g. daily, 1 g. daily having proved insufficient for this purpose. The dull pain due to tophi was relieved by probenecid, but tended to recur when the drug was withdrawn. Old tophi did not disappear, but on the other hand no new ones formed during the 5-year period of study. Phenylbutazone was added to the therapeutic regimen in the hope of reducing the requirements of ACTH, and this was in fact achieved. In this case colchicine in the maximum dosage tolerated by the patient has been

administered for 6 years, and ACTH therapy has been maintained for 4 years by means of careful adjustment of the dosage under strict observation. *C. E. Quin.*

Non-Articular Rheumatism

Non-Articular Rheumatism. (Les rhumatismes abarticulaires.) COLINET, E. (1954). *Acta physiother. rheum. belg.*, **9**, 204.

General Pathology

Sensitization of Sheep Erythrocytes by Abnormal Human Serums. Clinical Value and Significance of Agglutination Reaction. TAWIL, G. S., and ABD EL WAHAB, E. M. (1955). *Amer. J. clin. Path.*, **25**, 166. 21 refs.

The agglutination of sensitized sheep erythrocytes is one of a number of agglutination tests which give positive results in a high percentage of sera from cases of rheumatoid arthritis. The authors, working at the Faculty of Medicine, Abbassia, Cairo, have investigated the specificity of the reaction and its diagnostic value in detecting the early stages of this disease. The technique is described in detail. Readings were made at one hour after incubation at 37° C., and at 18 hrs at 15° C. A titre of 1 in 8 at one hr and of 1 in 32 at 18 hrs was taken as the deciding factor between "positive" or "negative".

Of 100 sera sent for routine testing by the Wassermann reaction (W.R.), 72 failed to agglutinate in any titre, sixteen agglutinated within the normal or negative range, four W.R.-positive and one W.R.-negative sera gave negative results, while seven sera from cases of unrelated [?] conditions (bilharzia, discoid lupus erythematosus, and one rheumatoid case) gave positive results. In a second group of 48 cases diagnosed as rheumatoid arthritis, 38 (79 per cent.) gave positive results and ten negative results. Of sera from six patients in whom rheumatoid disease had been present for less than 6 months, five gave positive reactions. Of thirty samples of serum from patients diagnosed as suffering from diseases other than rheumatoid arthritis [but including "rheumatic polyarthritis, menopausal arthritis, and gouty arthritis"] 25 gave negative and five positive results; of these latter, three were later reclassified as cases of rheumatoid arthritis, and the remaining two were diagnosed as cases of osteo-arthritis of the knee and "recurrent rheumatic polyarthritis" respectively. A fourth group of fifteen cases of various renal lesions gave ten positive results, while in sera from forty cases of rheumatic heart disease there were 34 with positive results. Lastly, the sera from fifteen cases of diverse hepatic disorders all reacted positively.

The authors discuss the nature of the reaction. The agglutinating-enhancing action was in no way modified whether the sera were absorbed with washed sheep erythrocytes or sheep erythrocytes sensitized with amboceptor. Serum lipids play no part in the reaction, but it is suggested that a change involving protein metabolism in the liver is a significant feature. The rheumatoid factor responsible for these reactions is present in small amounts as a constituent of normal serum. The authors conclude that while the results of this test may be useful in confirming a diagnosis of rheumatoid arthritis, they cannot be considered in any way as specific to the disease. *Harry Coke.*

Orientating Study on the Synovial Fluid with reference to the effect of Compound F. [In English.] KULONEN, E., and MAKINEN, P. (1955). *Acta rheum. scand.*, **1**, 89. 4 figs, 15 refs.

Urinary Excretion of 17-Ketosteroids during the Administration of Sodium Salicylate. (Sul comportamento dei 17-chetosteroidi urinari durante somministrazione di salicilato di sodio.) GREGORIS, L., and DRUDI, C. (1955). *Settim. med.*, **43**, 76. 17 refs.

Disturbances of Liver Function in Chronic Rheumatic Disease. (Störungen der Leberfunktion bei chronisch-rheumatischen Erkrankungen.) GAMP, A., GROS, H., KIRNBERGER, E. J., and BOPP, A. (1955). *Dtsch. med. Wschr.*, **80**, 782. 37 refs.

Role of the α-Haemolytic Streptococcus in the Aetiology of Acute Rheumatism. (Role du streptocoque hémolytique A dans l'étiologie du rhumatisme articulaire aigu.) COSTE, F., BASSET, G., and CHEVALLIER, J. (1955). *Bull. Acad. nat. Méd.* (*Paris*), **139**, 204.

Problem of Rheumatic Activity. Evaluation of Some Laboratory Methods. [In English.] SUAREZ, R. M., and SUAREZ, R. M., JR. (1955). *Bol. Asoc. med. P. Rico*, **47**, 51. 1 fig., 8 refs.

Effect of Serum and Certain Serum Electrolytes on the Activity of Testis Hyaluronidase in Carbonic Acid-Bicarbonate Buffer, *p*H 7·4. [In English.] THUNE, S., and TRUEDSSON, E. (1955). *Acta rheum. scand.*, **1**, 47. 8 figs, 15 refs.

Electrophoretic Analysis of Serum Proteins in Chronic Rheumatic Diseases. COKE, H. (1955). *Rheumatism*, **11**, 27. 3 figs, 9 refs.

ACTH, Cortisone, and Other Steroids

Changes in Plasma Levels of 17-Hydrocorticosteroids during the Intravenous Administration of ACTH. I. A Test of Adrenocortical Capacity in the Human. EIK-NES, K., SANDBERG, A. A., NELSON, D. H., TYLER, F. H., and SAMUELS, L. T. (1954). *J. clin. Invest.*, **33**, 1502. 4 figs, 9 refs.

At the University of Utah College of Medicine, Salt Lake City, the changes in the plasma level of 17-hydroxycorticosteroids was studied in 39 normal subjects and in six selected patients with adrenocortical insufficiency during the intravenous administration of ACTH of various potencies in 500 ml. saline or glucose in water. The subjects were in the fasting state, and none was studied more often than every 10 days. Plasma 17-hydroxycorticosteroid levels were determined by a modification of the method of Nelson and Samuels.

Maximal stimulation of the adrenal cortex was induced by the infusion of 15 to 25 i.u. ACTH over 6 hrs. The administration of 50 i.u. ACTH did not produce a significantly different response, nor did the infusion of a total of 25 i.u. ACTH over periods of 2, 4, 6 or 8 hrs produce any significant difference in the rate of increase in the plasma 17-hydroxycorticosteroid level. The values increasing proportionately to the mean. If the infusion were spread over 8 hrs, the plasma level at the end of the infusion did not differ significantly from that at 6 hrs, while if infusion was continued over many hours the plasma level reached a plateau which was maintained for as long as the infusion was continued. Plasma steroid levels returned to normal within 6 hrs of the cessation of the infusion of ACTH.

The response of the same subject to a standard test of 25 i.u. ACTH given over 6 hrs on different occasions showed considerable variation, which did not seem to be dependent on the control level of plasma 17-hydroxycorticosteroids, or on the animal source of ACTH or its method of preparation. In subjects showing symptoms of Addison's disease there was a decreased response to the test even when the plasma level of 17-hydroxycorticosteroids before infusion of ACTH was within normal limits. *Norval Taylor.*

Action of Chlorpromazine on Diencephalic Sympathetic Activity and on the Release of Adrenocorticotrophic Hormone. HOLZBAUER, M., and VOGT, M. (1954). *Brit. J. Pharmacol.*, **9**, 402. 9 refs.

The sedative action of chlorpromazine has been attributed to its inhibition of sympathetic diencephalic centres, or to its prevention of the release of ACTH in conditions of stress, that is, inhibition of hypothalamic activity. Working in the Department of Pharmacology, University of Edinburgh, the authors have investigated the action of the drug upon hypothalamic activity in cats, dogs, and rats. A dose of 40 mg. morphine per kg. body weight given subcutaneously to a cat causes excitement, the amount of noradrenaline in the hypothalamus is depleted, and impulses passing in the splanchnic nerves cause a discharge of amines from the adrenal medulla; no discharge of amines occurs when the adrenal gland has been denervated. Cats in which one adrenal had been denervated 3 weeks previously were given doses of morphine, nalorphine, and chlorpromazine and killed 4 to 5 hrs later. Extracts prepared immediately from the hypothalamus and adrenal glands were purified by paper chromatography and assayed for amines and noradrenaline activity on the blood pressure of rats anaesthetized with urethane and treated with atropine and hexamethonium. It was shown that chlorpromazine alone caused no release of noradrenaline; two doses, totalling 25 mg. per kg. body weight, given respectively before and 2 hrs after the morphine, did not affect the release of noradrenaline from the hypothalamus and the innervated adrenal. The morphine antagonist nalorphine completely prevented the release under the same conditions.

In two cats in which one superior cervical ganglion had also been removed, the pupils responded to circulating adrenal medullary amines towards the end of the experiment, showing that the adrenolytic action of chlorpromazine was not very powerful. In the chloralosed dog the adrenolytic action of 1·5 mg. chlorpromazine per kg. passed off in 30 minutes; at no time was there evidence of blockage of transmission in sympathetic ganglia.

The effect of chlorpromazine on the release of ACTH by stress was investigated in rats given doses of 10 to 15 mg. per kg.; one-half to 3 hrs later the viscera were exposed under urethane anaesthesia, the mesentery handled for 2 minutes, and the abdomen closed. After a further hour the rats were killed and the ascorbic acid content of the adrenal glands determined and compared with the results in control groups given saline, chlorpromazine, or "stress" alone. No significant protective action of chlorpromazine upon the depletion of adrenal ascorbic acid was observed. In rats trained to receive injections of saline without emotional response chlorpromazine alone caused some release of ascorbic acid and did not prevent the further release caused by an injection of adrenaline.

It is concluded that the shock-preventing action of chlorpromazine is not a result of inhibition of the adrenal defence mechanism, but is perhaps due to the metabolic effects of the drug. *L. G. Goodwin.*

Anti-Inflammatory Mechanism of Hydrocortisone (Compound F). MENKIN, V. (1954). *Science*, **120**, 1026. 4 figs, 12 refs.

In an investigation of the effects of hydrocortisone on the inflammatory mechanism, carried out at Temple University School of Medicine, Philadelphia, acute inflammation was induced in dogs by the intrapleural injection of 1·5 ml. turpentine under pentobarbitone anaesthesia. Test animals received 10 to 20 mg. hydrocortisone as the free alcohol into the same site daily for 3 to 4 days thereafter, while control dogs received injections of saline. A sample of exudate was then withdrawn from the chest cavity of dogs of each group and the activity of the leucotaxine and leucocytosis-promoting factor (L.P.F.) extracted from the fluids assessed. In the test animals the activity of leucotaxine in regard to its ability to increase the permeability of small vessels and the outward migration of leucocytes in rabbits was reduced, while that of the L.P.F. in causing a rise in the leucocyte count and the discharge of immature polymorphonuclear leucocytes into the circulation in dogs was about one-half that of L.P.F. derived from controls.

The activity of L.P.F. was not affected by mixing with hydrocortisone *in vitro*, which suggests that *in vivo* hydrocortisone prevents the injured cells in the inflamed area from forming L.P.F. rather than interacting directly with preformed L.P.F. at the site of inflammation. On the other hand, previous work by the author has shown that leucotaxine is to a large extent inactivated by cortisone or hydrocortisone *in vitro*, but the steroids may also prevent its formation in injured cells.

The author concludes that hydrocortisone impairs the

activity of the injured cell in producing some if not all of the specific chemical factors involved in inflammation. *Norval Taylor.*

Aldosterone in Urine of Normal Man and of Patients with Oedema. AXELRAD, B. J., CATES, J. E., JOHNSON, B. B., and LUETSCHER, J. A. (1955). *Brit. med. J.*, **1**, 196. 19 refs.

The study reported here from Stanford University School of Medicine, San Francisco, was devoted largely to the determination of optimum conditions for the recovery of the aldosterone-like steroids occurring in human urine.

Extracts with chloroform were made at *p*H 6·5 and at *p*H 1·0, and also after 24 hrs at *p*H 1·0 and room temperature. Further hydrolysis was also effected with β-glucuronidase. For bio-assay, groups of nine adrenalectomized rats were used, the effect of the extract on the urinary potassium: sodium ratio being compared with that of varying doses of deoxycortone acetate.

Extracts made at *p*H 6·5 showed only insignificant sodium-retaining activity, but when the urine was acidified to *p*H 1·0 before extraction significant activity was found in the urine of a patient with nephrosis and in one with hepatic cirrhosis, but not in that of a healthy subject. No sodium-retaining activity was lost by washing the extract with dilute sodium hydroxide solution. Extracts of urine from healthy adults on normal diet made after standing at room temperature for 24 hrs at *p*H 1·0 showed strong sodium-retaining activity, as also did similar extracts of the urine of normal adults after salt restriction. Extracts made after glucuronidase hydrolysis for 48 hrs also showed increased activity, but in general the increase was smaller than after 24 hrs at *p*H 1·0. The chromatographic properties of the material studied left no doubt that it was aldosterone. *C. L. Cope.*

Effect of Salicylate and of *para*-Aminobenzoate on the Eosinophil Response to ACTH. O'CONNELL, P. A., ROY, A., and MASSELL, B. F. (1955). *Amer. J. med. Sci.*, **229**, 150. 3 figs, 31 refs.

Since the advent of ACTH (corticotrophin) and cortisone, numerous attempts have been made to determine whether other drugs used in the treatment of the rheumatic disorders act, like ACTH, by stimulation of the adrenal cortex. The results are reported from the Children's Medical Center (Harvard Medical School), Boston, of a study of the effect on adrenal cortical function as indicated by changes in the eosinophil count, of the administration of sodium salicylate and *para*-aminobenzoate to 132 patients convalescent from rheumatic fever, chorea, or mild rheumatoid arthritis. All but three were between 5 and 16 years old.

Neither of the drugs had any effect on the eosinophil count when given alone in various dosages, nor was any effect observed when both were given together in doses of 60 to 90 mg. of each per kg. bodyweight daily. However, the eosinopenic response to the injection of 12 units ACTH in six doses at hourly intervals, which was not affected by the administration of either drug in doses of 60 to 90 mg. per kg. daily, was significantly increased by the administration of 100 to 125 mg. of sodium salicylate per kg. daily or of both drugs together in doses of 60 to 90 mg. per kg. daily. *Oswald Savage.*

Effects of Aldosterone (Electrocortin) and of 9-α-Fluoro Hydrocortisone Acetate on Rheumatoid Arthritis: Preliminary Report. WARD, L. E., POLLEY, H. F., SLOCUMB, C. H., HENCH, P. S., MASON, H. L., MATTOX, V. R., and POWER, M. H. (1954). *Proc. Mayo Clin.*, **29**, 649. 7 figs, 30 refs.

Aldosterone and 9-α-fluoro hydrocortisone acetate, two recently discovered steroids, were administered at the Mayo Clinic to a number of patients with rheumatoid arthritis, and the authors here report the clinical and metabolic effects observed.

Aldosterone, derived from animal adrenal tissue, was administered to two patients by intramuscular injection for 6 days each. The daily dose in the first case was 800 μg., and in the second 1,000 μg. These doses had no anti-rheumatic effect on either patient but did produce some retention of sodium, chloride, and fluid, as would be expected. 9-α-fluoro hydrocortisone acetate, a synthetic product, was administered to three patients in doses of 4 mg., 6 mg., and 8 mg. respectively daily for 12 to 28 days. With these moderate doses rheumatic symptoms were lessened, but troublesome retention of sodium, chloride, and fluid was produced and potassium loss was increased. Clinically, oedema and hypopotassaemia were caused, and a tendency was noticed also towards the development of hypochloraemia and alkalosis.

Despite the apparent lack of antirheumatic activity of aldosterone and the obvious therapeutic limitations placed on 9-α-fluoro hydrocortisone acetate by its side-effects, the authors consider that the fact that such marked differences in characteristics and potency exist between these and other steroid substances of natural or synthetic origin strongly suggests that superior compounds will in due course be developed for the control of the clinical course of rheumatoid arthritis, and so render its management easier. *W. S. C. Copeman.*

Clinical Aspects of the Arthritis provoked by Deoxycortone. (Aspects cliniques des arthrites provoquées par la désoxycorticostérone.) GENNES, L. DE, BRICAIRE, H., and VILLIAUMEY, J. (1955). *Rev. Rhum.*, **22**, 1. 6 refs.

In this paper, which was read before the Ligue française contre le Rhumatisme in November, 1954, the authors discuss the effect of administration of deoxycortone acetate (DCA) to patients with Addison's disease. Of 120 such patients treated with DCA, 26 developed joint symptoms, and of these, six complained of severe arthralgia in various joints, sixteen developed polyarthritis similar to that of rheumatic fever, and four had painful contractures with severe limitation of movement. These disturbances developed within days or weeks of the start of treatment, whether DCA was given by multiple injections or by subcutaneous implantation. With

cessation of such treatment there was a slow improvement in the joint condition. Recurrence could often be provoked by a further course of DCA. Cortisone helped to control the arthritic manifestations, and the authors consider that a good case can be made out for the use of cortisone instead of DCA in the management of these cases to prevent the occurrence of painful and disabling polyarthritis. A number of representative case histories are given. *G. W. Csonka.*

Effects of Cortisone and Antibiotics on Lethal Action of Endotoxins in Mice. GELLER, P., MERRILL, E. R., and JAWETZ, E. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **86**, 716. 17 refs.

Working at the University of California School of Medicine, San Francisco, the authors have investigated the protective effects of cortisone in mice given lethal amounts of an endotoxin. A single dose of crude endotoxin of *Escherichia intermedium*, sufficient to cause death in 80 to 100 per cent. of animals within 48 hours, was injected intraperitoneally into mice. The administration of a single dose of 5 mg. cortisone subcutaneously one hour before the endotoxin in some cases or simultaneously with it in others protected 60 to 90 per cent. of the animals from death, but failed to do so if injected one hour after the endotoxin. In view of reports of the reinforcing effect of some antibacterial drugs, chlortetracycline, penicillin, chloramphenicol, and streptomycin were administered in a wide range of doses, but only the last named in a dose of 2 mg. per mouse gave any protection against the endotoxin, and that inconsistently. Furthermore, cortisone given one hour before, and streptomycin given one hour after, the endotoxin resulted in a higher mortality than occurred when cortisone alone was used to protect the animals. It was also shown that penicillin was equally if not more active in interfering with the protective effect of cortisone. *B. Nordin.*

Therapy of the Nephrotic Syndrome. Sodium Restriction, Dextran, and Corticotropin (ACTH) Alone or Combined with Nitrogen Mustard. GREENMAN, L., WEIGAND, F. A., and DANOWSKI, T. S. (1955). *Amer. J. Dis. Child.*, **89**, 169. 1 fig., 35 refs.

At the Pittsburgh Children's Hospital (University of Pittsburgh School of Medicine) thirty children suffering from the nephrotic syndrome were treated with ACTH (corticotrophin) in 25-mg. doses 6-hourly for a month and with a diet containing 2 to 9 mEq. sodium, 150 mEq. potassium, and 3 g. protein per kg. body weight per day, together with supplementary iron and vitamins. In addition, 25 patients received 0·3 mg. nitrogen mustard per kg., usually on the third day of treatment, and eighteen received infusions of Dextran (polyvinylpyrrolidone). An antibiotic, usually penicillin, was given throughout.

Of the thirty children, 22 appeared to be cured. This was attributed to the ACTH and the diet rather than to the other therapeutic measures, and the authors stress that the effect of ACTH was not only to promote diuresis—proteinuria was relieved and the biochemical findings in the blood returned to normal in the majority of cases. *Wilfrid Gaisford.*

Inhibition of Acute *X*-ray Damage by Cortisone. HOUGHTON, L. E., WALTER, J. B., and JONES, D. E. A. (1954). *Brit. med. J.*, **2**, 1313. 1 fig., 18 refs.

When a circular area of skin of the guinea-pig is irradiated with 6,000 *r* inflammatory changes occur, followed within 60 days by deep ulceration. In this paper the authors present evidence to show that if cortisone acetate is administered parenterally before and after such irradiation there is no serious damage to the skin within a similar period of time. A group of 38 guinea-pigs received a dose of 6,000 *r* to a circular area of skin, nineteen of the animals being given cortisone parenterally and nineteen serving as controls. The field was 2·6 cm. in diameter, and the *x*-ray beam was generated at 50 kV. The animals received 3,000 *r*, followed in 48 hours by a further 3,000 *r*. A dose of 10 mg. cortisone acetate was injected into the anterior abdominal wall 24 hours before the first exposure and repeated each morning throughout the period of observation. In the cortisone-treated animals early erythema was reduced and epilation was delayed; there was no shrinkage of the irradiated areas, although this was marked in the control animals. Deep ulcers developed in all the control animals; by contrast only two of the cortisone-treated group developed deep ulcers and these were small and healed rapidly. *D. Waldron Smithers.*

Simultaneous Administration of Cortical Steroids and ACTH: the Effect on Adrenal Weight and Cholesterol Concentration. RAWLS, W. B., BAKER, E., TICHNER, J. B., and GOLDZIEHER, J. W. (1954). *J. Lab. clin. Med.*, **44**, 506. 11 refs.

The effect of administration of cortical steroids on the weight and cholesterol concentration of the adrenal glands of hypophysectomized rats was investigated at St. Clare's Hospital, New York. Cortisone, hydrocortisone, and corticosterone in a dosage of 5 mg. daily, with and without 1 mg. ACTH (corticotrophin) in aqueous solution three times daily, were the drugs used, each combination of steroid and ACTH being given to different groups of animals 7 days after hypophysectomy and this treatment continued for 15 days.

It was found that cortisone, hydrocortisone, and corticosterone did not reduce the weight of the adrenal glands, as compared with those of hypophysectomized control animals. Simultaneous administration of ACTH and steroids prevented adrenal atrophy, while ACTH, either alone or in combination with the steroids, caused regeneration and maintained cholesterol concentration of the adrenal glands in hypophysectomized animals.

The clinical implications of these findings are discussed. *D. G. Adamson.*

Treatment of Certain Forms of Pulmonary Tuberculosis with ACTH in association with Antibiotics. (Le traitement de certaines formes de tuberculose pulmonaire par l'association d'ACTH et d'antibiotiques.) LEDERER, J., MANNES, P., DERRIKS, R., and NICAISE, R. (1955). *Bull. Soc. méd. Hôp., Paris*, **71**, 273. 20 refs.

The authors describe four clinically diverse cases of pulmonary tuberculosis which had failed to respond to,

or had relapsed after, standard treatment with antibiotics, but in which the administration of ACTH (corticotrophin) was, in their opinion, responsible for a favourable outcome in at least two of the cases, namely, one of miliary tuberculosis with meningitis and one of tuberculous bronchopneumonia; in both of these recovery began only when ACTH was given. They were particularly struck by the rapidity of closure of cavities, present in three of the cases, and the conversion of the sputum. ACTH was also of benefit in reducing drug hypersensitivity, although it failed in one case to control a rash due to streptomycin.

The authors recognize the considerable divergence of views on the value of ACTH in pulmonary tuberculosis. They agree that large doses are definitely dangerous and in treating these four cases they limited the dosage to 5 to 10 mg. daily intravenously, or 5 to 20 mg. intramuscularly. Considerable stress is placed on the safety and clinical value of these minute doses, but they must of course always be supplemented with the usual antibiotic therapy. The hormone is best given continuously for a period of 6 to 12 weeks, and is to be preferred to cortisone.

The possible mode of action of ACTH is discussed at some length. *Paul B. Woolley.*

Response of Plasma 17-Hydroxycorticosteroids to Salicylate Administration in Normal Human Subjects. DONE, A. K., ELY, R. S., and KELLEY, V. C. (1955). *Metabolism*, **4**, 129. 4 figs, bibl.

Normal adult human subjects given salicylates in usual therapeutic doses failed to show consistent elevations in circulating levels of 17-hydroxycorticosteroids (17-OH-CS); indeed, these levels frequently were found to be reduced significantly. Salicylate administration was, in many cases, accompanied by greater fluctuations in plasma concentrations of these cortical steroids than were found as normal diurnal variations. Both increases and decreases in steroid concentrations were significantly greater on days of salicylate administration than on control days. The urinary excretion of 17-ketosteroids was unchanged, while significant reduction in the urinary output of 17-OH-CS was observed. These data suggest that, if increased adrenal steroid production follows salicylate administration, it is counter-balanced by an increased rate of removal of steroids from the circulation by a means other than urinary excretion.

There was no consistent correlation between eosinophil and steroid responses to salicylate.—[*Authors' summary.*]

Long-Term Sequelae of Treatment with ACTH or Cortisone in Cases of Pulmonary and Pleural Tuberculosis. (Suites éloignées de quelques traitements par l'ACTH ou la cortisone dans les tuberculoses pulmonaires et pleurales.) KLOTZ, H. P., and GUEZ, A. (1955). *Bull. Soc. méd. Hôp., Paris*, **71**, 361.

The authors report from the Hôpital Bichat, Paris, the results of the treatment of 15 cases of pulmonary and pleural tuberculosis with ACTH (corticotrophin) or cortisone in addition to the usual antituberculous drugs. ACTH was given in a dose of 10 mg. by perfusion over 6 hours in a glucose serum, or in doses of 100 to 200 mg. intramuscularly twice daily; cortisone was given in a dosage of 25 to 50 mg. per day. The average length of each course was 10 days.

The 15 cases were divided into four groups according to the result of treatment:

(1) Six showed marked improvement in the tuberculous and general state;
(2) Three showed improvement in the local tuberculous condition;
(3) In four no improvement occurred; and
(4) In two cases there was improvement in some aspects of the disease but deterioration in others.

The six patients showing marked improvement did so rapidly, although the disease was widespread and all were gravely ill. The three showing only local change included two cases of serofibrinous disease. After administration of ACTH there was a pronounced diminution in the amount of fluid and considerable radiological improvement. Of the two cases undergoing only partial improvement, in one there were definite radiological signs of healing, but at the same time the general condition of the patient was thought worse after treatment. In the other there was a rise in temperature lasting 3 weeks after the first course of ACTH and another rise lasting 10 days after the second course of the hormone.

Summing up, the authors conclude that ACTH is probably most efficacious in cases of acute inflammatory disease and in patients with pyopneumothorax, although in the present series it was of most value as a means of arresting the spread of the disease. If the disease is very advanced these hormones have no influence on the final prognosis, although death may be delayed for a few months. They point out that hormonal treatment prevented the formation of adhesions in their cases of serofibrinous tuberculosis, and was also of value in the management of cases with purulent effusion, the combined use of ACTH and chemotherapy preparing the way for surgery. ACTH by itself is of course not curative of tuberculosis, although it enhances the action of streptomycin, PAS, and isoniazid in most forms of the disease. *Thomas Marmion.*

Effect of Adrenaline on Adrenocortical Secretion. HUNTER, J. D., BAYLISS, R. I. S., and STEINBECK, A. W. (1955). *Lancet*, **1**, 884. 1 fig., 19 refs.

In a study at the Postgraduate Medical School of London of the effect of adrenaline on adrenocortical activity the eosinopenia caused by adrenaline was compared with that caused by corticotrophin; the plasma levels of 17-hydroxycorticosteroids were also determined during the 30 minutes after subcutaneous injection of 0·3 to 0·5 mg. adrenaline and during the 4 hrs following intravenous injection of 30 units of corticotrophin. After the injection of adrenaline the eosinophil count fell by amounts ranging from 17 to 84 per cent. (mean 55 per cent.) of normal, the minimum being reached 2 to 4 hrs after the injection. No consistent change in the plasma level of 17-hydroxycorticosteroids was observed. There was no consistent change in the eosinophil count in

response to injection of saline solution in controls. When corticotrophin was injected the maximum fall in the eosinophil count occurred 3 to 4 hrs later, and the plasma level of 17-hydroxycorticosteroids rose consistently. The results showed that the eosinopenia caused by adrenaline is unrelated to a rise in the plasma level of 17-hydroxycorticosteroids. *P. A. Nasmyth.*

Adrenocortical Capacity and the Metabolism of Cortisol in Elderly Patients. TYLER, F. H., EIK-NES, K., SANDBERG, A. A., FLORENTIN, A. A., and SAMUELS, L. T. (1955). *J. Amer. Geriat. Soc.*, **3**, 79. 2 figs, 7 refs.

The urinary 17-ketosteroid excretion of elderly patients is less than that of young adults, and it has been suggested that this is because adrenal cortical function diminishes with increasing age. The authors, working at the University of Utah College of Medicine, Salt Lake City, have estimated the 17-hydroxycorticosteroid content of the plasma of patients aged 66 to 92 years, excluding any with acute inflammatory or endocrine disorders. The mean morning plasma 17-hydroxycorticosteroid level in a number of these patients was higher than in a group of young adults [the size of the group is not stated], but the difference was not statistically significant. After an infusion of ACTH (corticotrophin), however, the mean level was significantly higher in five of the older subjects than in a larger group of young adults. Similarly, after the infusion of 1 mg. hydrocortisone per kg. body weight the level of 17-hydroxycorticosteroids in the blood rose higher in the older group; however, the rate of removal of hydrocortisone from the blood was the same in both groups at first, though it fell off later in the older group.

The conclusion is drawn that there is no deficiency of secretion or metabolism of 17-hydroxycorticosteroids in the elderly, the differences observed between the blood levels of younger and older subjects in the various circumstances studied being explained as due to differences in the volume of distribution. These might be related to differences in body fat distribution, although no correlation between the effect of an infusion of hydrocortisone on the plasma level and the degree of obesity of the subject was observed. Whatever the explanation it might be expected that smaller therapeutic doses of ACTH and cortisone would be needed by elderly patients than by young adults. *J. N. Agate.*

Fluorohydrocortisone and Chlorohydrocortisone Highly Potent Derivatives of Compound F. GOLDFIEN, A. L., LAIDLAW, J. C., HAYDAR, N. A., RENOLD, A. E., and THORN, G. W. (1955). *New Engl. J. Med.*, **252**, 415. 11 figs, 7 refs.

It has been shown that 9-α-chlorohydrocortisone and 9-α-fluorohydrocortisone have both glucocorticoid and mineralocorticoid activity. The present paper from the Peter Bent Brigham Hospital, Boston, reports a comparative study of the metabolic and therapeutic effects of these two compounds. Chemical determinations and eosinophil counts were carried out by standard methods.

Preliminary tests on a patient with Addison's disease showed that the chloro- and fluoro- derivatives had a considerably more potent action than either cortisone or hydrocortisone (Compound F) in respect to both their glycogenic and sodium-retaining effects, and produced a greater and more prolonged eosinopenia. In a metabolic experiment on a patient with Addison's disease who was maintained on a constant diet, 3 mg. chlorohydrocortisone and 0·25 mg. fluorohydrocortisone were found to be equivalent to 1 mg. deoxycortone. In another similar patient fluorohydrocortisone was found to be as potent in sodium-retaining properties as aldosterone and to have a more prolonged action; a similar observation was made in a subject with normal adrenal function.

Clinically it was shown that Addisonian patients could be maintained satisfactorily on comparatively small doses of fluorohydrocortisone given by mouth (in the ratio of approximately 1 mg. fluoro- compound to 20 mg. cortisone or hydrocortisone. On these small doses no 17-hydroxycorticoids could be detected in the urine by the Porter–Silber reaction. Thus effective substitution therapy with adrenal hormones can be continued during the administration of ACTH for the diagnostic evaluation of adrenocortical function. The authors conclude that satisfactory inhibition of the adrenal cortex can be achieved in normal subjects, and in female patients with the adrenogenital syndrome, by the oral administration of 1 to 2 mg. fluorohydrocortisone per day.

Nancy Gough.

Studies in Surgical Endocrinology. 1. The Urinary Excretion of 17-Hydroxycorticoids, and Associated Metabolic Changes, in Cases of Soft Tissue Trauma of Varying Severity and in Bone Trauma. MOORE, F. D., STEENBURG, R. W., BALL, M. R., WILSON, G. M., and MYRDEN, J. A. (1955). *Ann. Surg.*, **141**, 145. 18 figs, bibl.

This paper reports the results of investigation of the urinary excretion of 17-ketosteroids and 17-hydroxycorticoids in relation to clinical and metabolic events in eleven patients undergoing various types of surgical operation at the Peter Bent Brigham Hospital (Harvard Medical School), Boston. Nitrogen, potassium, sodium, and, in some instances, chloride balances were performed, and total body water and total exchangeable sodium and potassium were determined. Similar studies were carried out on a control group of normal subjects of constant weight, the changes produced by a period of starvation being also noted, since post-traumatic changes are frequently contrasted with those of starvation.

In three cases of appendicectomy, including one in which there had been a ruptured appendix with subsequent pelvic abscess, the changes in 17-ketosteroid excretion were insignificant, but excretion of 17-hydroxycorticoids increased after operation as the eosinophil count fell; in the septic case this was maintained until the abscess was drained being paralleled by high nitrogen loss and a prolonged catabolic phase, with loss of 12 per cent. of bodyweight.

In five cases of soft-tissue trauma there was, in general fair correlation between clinical severity, nitrogen loss,

the fall in the eosinophil count, and the rise in 17-hydroxycorticoid excretion, but 17-ketosteroid excretion could not be related to the other events. In two cases the characteristic pattern of 17-hydroxycorticoid excretion was distorted; the first, a case of second-degree burn, showed an unexpectedly low hormone output for the first few days, and in the second, a case of cancer of the breast, the rise in hormone output was prolonged in spite of the post-operative eosinophil count showing the normal changes.

Finally, in three cases of trauma of bone there was a consistent tendency to an inverse correlation between 17-hydroxycorticoid excretion and the eosinophil count. Case histories and detailed charts are presented for all the cases discussed. *Nancy Gough.*

Adrenocortical Function during Long-Term Cortisone Therapy. Further Observations. FREDELL, E. W., JOHNSON, H. P., KRUPP, M. A., ENGLEMAN, E. P., and MCGRATH, A. K. (1955). *Arch. intern. Med.*, **95**, 411. 3 figs, 18 refs.

At the Veterans Administration Hospital, San Francisco, adrenocortical function was assessed in nineteen patients who had been receiving treatment with cortisone for periods of one to 4 years, by determining the eosinophil count and the level of urinary 17-ketosteroid and urinary corticoid excretion after 5 consecutive days of intravenous infusion of ACTH (corticotrophin). Adrenocortical response was considered adequate if two of the following criteria were met:

(1) a decrease of more than 60 per cent. in the number of eosinophil granulocytes;
(2) an increase of more than 50 per cent. in urinary 17-ketosteroid excretion;
(3) an increase of more than 50 per cent. in urinary corticoid excretion.

The results, which are presented in several ways in tables and diagrams, showed that there was a slight tendency for a longer period of stimulation with corticotrophin to be necessary in order to evoke an adequate adrenal response when cortisone therapy had been prolonged. The authors conclude that the adrenal cortex which has been suppressed by the administration of cortisone is still responsive to stimulation with ACTH. It was noted that long-term cortisone therapy had no effect on thyroid function.

[Unfortunately the results are presented in a form which makes them difficult to assess.] *C. L. Cope.*

Anticortisol Action of Aldosterone. SELYE, H. (1955). *Science*, **121**, 368. 7 refs.

The concept that the course of various biological phenomena, such as inflammation, is regulated by a balance between the opposing activities of two types of corticoid secreted by the adrenal cortex—the glucocorticoids and the mineralocorticoids—is an essential part of the theory of the general adaptation syndrome. However, there has hitherto been no direct proof that the adrenal cortex secretes effective quantities of any mineralocorticoid comparable to the synthetic substance deoxycortone. The recent isolation of aldosterone appeared to fill this gap, but it still remained to be determined whether aldosterone is actually an antagonist of glucocorticoids.

To this end experiments were carried out at the University of Montreal on 96 female rats which had undergone bilateral adrenalectomy. They were fed throughout the experimental period on a standard diet without special salt supplements. Starting on the day of adrenalectomy, 400 μg. cortisol (hydrocortisone) microcrystals and 20 μg. aldosterone were injected daily into ten rats, six received the aldosterone alone, 40 were given the cortisol alone, and 40 were given no treatment. For the quantitative assessment of inflammation "granuloma pouches" were prepared 48 hours later by the injection of 25 ml. air under the dorsal skin followed immediately by the injection of 0·5 ml. 1 per cent. croton oil into the air space. The surviving animals were killed on the fourteenth day after adrenalectomy. The mean gain or loss of weight, volume of inflammatory exudate, and weight of the spleen and thymus gland were determined and mortality calculated for each group. Under these conditions aldosterone diminished slightly but significantly the loss of weight and inhibition of formation of inflammatory exudate caused by cortisol, but did not significantly suppress the involution of the thymus and the spleen.

In a second experiment on 36 female rats (in which the "granuloma pouches" were prepared first, hormone treatment beginning 48 hours later simultaneously with bilateral adrenalectomy) the dose of aldosterone was increased to 25 μg. twice daily and additional control groups were treated with cholesterol and with deoxycortone acetate. In this dosage aldosterone was shown to be equally effective with deoxycortone in inhibiting the effects of cortisol, although in other respects the mineralocorticoid activity of aldosterone has been estimated to be 25 to 125 times greater than that of deoxycortone. Cholesterol had no inhibitory effect.

P. A. Nasmyth.

Cushing's Syndrome with Bilateral Adrenal Hyperplasia: a Study of the Plasma 17-Hydroxycorticosteroids and the Response to ACTH. GRUMBACH, M. M., BONGIOVANNI, A. M., EBERLEIN, W. R., VAN WYK, J. J., and WILKINS, L. (1955). *Bull. Johns Hopk. Hosp.*, **96**, 116. 3 figs, 32 refs.

The difficulties of establishing a laboratory diagnosis of Cushing's syndrome are discussed. At Johns Hopkins Hospital, Baltimore, the authors determined the plasma level of free and conjugated 17-hydroxycorticosteroids in four patients with Cushing's syndrome, and compared it with that in fourteen cases of the adrenogenital syndrome; four of Addison's disease, and in a number of subjects with presumably normal adrenal function.

The mean level of free plasma corticoids in normal subjects was 8 μg. per 100 ml. and of the conjugated fraction 6·5 μg. per 100 ml. In the cases of Cushing's syndrome with adrenal hyperplasia the level of the free steroids was not always abnormally high, but when the conjugated fraction was determined in addition the total amount was always raised. In the cases of adrenogenital syndrome all values were low, and in those of Addison's

disease no measurable corticoids could be determined. After a 4-hr infusion of ACTH, there was a substantially greater rise in the level of circulating corticoids in two of the patients with Cushing's syndrome associated with adrenal hyperplasia than in normal subjects or in the cases of adrenogenital syndrome; in the patients with Addison's disease there was no response at all to the infusion of ACTH. *B. Nordin.*

Counteracting the Acute Radiation Syndrome with Corticotrophin (ACTH). TABER, K. W. (1955). *Amer. J. Roentgenol.*, **73**, 259. 1 fig., 27 refs.

Writing from the Memorial General Hospital, Elkins, West Virginia, the author claims that good results in the relief of radiation sickness can be obtained by the administration of 10 mg. ACTH daily, this treatment being continued until symptoms are alleviated, and the course repeated if necessary. The tabulated results in 416 of the author's cases show that 47·6 per cent. obtained prompt complete relief, 34·1 per cent. delayed complete relief, 16·4 per cent. delayed incomplete relief, and 2 per cent. [not 19·2 per cent. as stated] no definite benefit. The author concludes that the use of ACTH has made it possible "to administer radiation therapy more intensively and in much higher doses through a grid without unwarranted discomfort to the patient". *E. Stanley Lee.*

Corticotropin in Temporal Arteritis. [In Danish.] BARFOED, P. (1955). *Nord. Med.*, **53**, 931. 20 refs.

Report of a case in a 71-year-old man with severe impairment of vision in both eyes and bilateral temporal arteritis. Treatment with corticotropin improved the general state but the eye signs and symptoms were unaffected. *E. Godtfredsen.*

Inhibitory Effect of Vitamin B_{12} on Cortisone and ACTH. [In English.] LOVGREN, O., NORMAN, A., and WINQVIST, G. (1955). *Acta rheum. scand.*, **1**, 106. 1 fig., 7 refs.

Failure of ACTH and Adrenal Corticoids to alter the Course of Hepatic Coma in Advanced Portal Cirrhosis. SKLAR, M., and YOUNG, I. I. (1955). *Amer. J. med. Sci.*, **229**, 138. 16 refs.

Colorimetric Reaction for the Estimation of Cortisone, Hydrocortisone, Aldosterone, and Related Steroids. CLARK, I. (1955). *Nature (Lond.)*, **175**, 123. 1 fig., 2 refs.

Therapeutic Indications for the Corticotrophic and Adrenal Hormones. (Indications thérapeutiques respectives des hormones corticotrope et surrénale.) COSTE, F., and DELBARRE, F. (1955). *Rev. Rhum.*, **22**, 93.

Other General Subjects

Role of Physical Medicine in Relief of Certain Pain Mechanisms of Shoulder. RUSSEK, A. S. (1954). *J. Amer. med. Ass.*, **156**, 2575.

The author first points out that the nature of a lesion causing pain in the shoulder must be accurately diagnosed before treatment can be prescribed. He suggests that in 75 per cent. of patients shoulder pain is due either to postural stress or to adaptive changes in the shoulder and shoulder girdle secondary to some specific lesion. The scapulo-costal syndrome, with pain in the neck which may radiate down the arm and to the sternum, is the result of postural stress. When symptoms are chronic there is persistent spasm of the trapezius. This is often treated by application of heat and massage, but the effect of such measures is transient only. Treatment is aimed at the relief of muscle spasm, postural re-education, and relief of the persistent postural pull on the muscle.

Adaptive changes are associated with loss of movement in the gleno-humeral joint, which may follow many lesions in the shoulder-joint, including acute bursitis, fractures, and rheumatoid arthritis. Treatment consists in relief of muscle spasm and application of heat and massage, which, in the author's view, must be followed by passive movements to the point of tolerance and even beyond. He emphasizes the palliative value of physiotherapy as a preliminary to restoration of function.

W. Tegner.

DCA-like Effects of Butazolidin in Normal Subjects and in a Patient with Addison's Disease. GABRIEL, J. B., KATZ, H. M., REIMAN, J., and LUGER, N. M. (1955). *Metabolism*, **4**, 119. 4 figs, 15 refs.

The effect of phenylbutazone ("butazolidin") on sodium and water metabolism was compared with that of deoxycortone acetate (DCA) in three healthy subjects with "minimum arthritic involvement" and one patient with Addison's disease at the Veterans Administration Hospital, Brooklyn, New York. A constant diet was given for a period of 6 days and a "half-aliquot of the daily diet" of each patient was analysed for the sodium and potassium content by the wet-ashing method of Wallace; the patient's plasma volume was determined by the use of azovan ("Evans") blue, and a Janke flame photometer was employed for estimating the plasma sodium and potassium levels.

Phenylbutazone was given in a dosage of 800 mg. daily for 6 to 12 days; this was followed by a rest period of 8 to 12 days and then DCA in oil in a daily dosage of 20 mg. was given intramuscularly for 4 to 8 days. In all four subjects administration of phenylbutazone was accompanied by sodium and water retention, this being most marked in the patient with Addison's disease. In the three healthy subjects sodium and water retention was similar in degree to that observed after administration of DCA. Phenylbutazone did not appear to have any effect on glucose metabolism, potassium excretion, or the eosinophil count.

The plasma volume increased in two of the healthy subjects by 7 and 12 per cent. respectively and in the patient with Addison's disease by 25 per cent. The authors suggest that phenylbutazone by mouth may be a possible substitute for DCA in the treatment of Addison's disease.

I. McLean Baird.

Role of Peripheral Circulatory Disorders in Rheumatic Diseases. (Die Rolle der peripheren Durchblutungsstörungen bei rheumatischen Erkrankungen.) RATSCHOW, M. (1955). *Rheumaforsch.*, **14**, 76. 26 refs.

At the Municipal Medical Clinic, Darmstadt, the oscillometric readings, pulse tracings, and angiograms obtained from groups of patients suffering from different rheumatic diseases gave comparable results and suggested that rheumatic disorders are frequently associated with arterial damage. This usually takes the form of constriction, which in the author's opinion is hardly likely to be of nervous origin and may be due to collagen changes. In such cases, also, capillary permeability, as tested by reactive hyperaemia, was shown to be altered, the difference between arterial and venous capillary pressures in rheumatic patients being largely abolished. The author believes that much of the traditional therapy of rheumatism is designed to increase peripheral blood flow and the results of this study of 1,000 cases supports the view that vascular lesions do, in fact, exist in these patients.

[The author includes among the variety of rheumatic diseases investigated cases of "muscular rheumatism", a diagnosis which apparently still has an appeal to German clinicians.] *David Preiskel.*

Hydrocortisone in Lesions of Soft Tissue. CRISP, E. J., and KENDALL, P. H. (1955). *Lancet*, **1**, 476. 3 figs, 12 refs.

Local injection of hydrocortisone was tried at Guy's Hospital, London, in the treatment of 208 cases of soft-tissue inflammation, commonly termed "rheumatism". Among the conditions treated were tennis elbow, golfer's elbow, plantar fasciitis, olecranon and pre-patellar bursitis, acute and chronic soft-tissue lesions of the shoulder-joints, tenosynovitis, and Dupuytren's contracture. A suspension of 25 mg. hydrocortisone was mixed with 1,000 units of hyaluronidase dissolved in 2 to 5 ml. 2 per cent. procaine hydrochloride, and the mixture injected into the area of greatest local tenderness. In 80 per cent. of cases there was complete relief of symptoms, in 10 per cent. there was a recurrence, usually in less than 3 months, and in 10 per cent. the treatment was ineffective. This treatment was also given in 29 cases of acute traumatic joint effusion with complete relief of symptoms, usually within 72 hrs, in 21 cases, improvement in seven and no change in one case.

[As the authors state there is a natural history of spontaneous recovery in these conditions, although the period of painful incapacity is often long. A control series would have been interesting.] *Oswald Savage.*

Radiological Diagnosis of Peripheral Circulatory Disorders in Rheumatic Diseases. (Die Röntgendiagnostik peripherer Durchblutungsstörungen bei rheumatischen Erkrankungen.) LEB, A. (1955). *Z. Rheumaforsch.*, **14**, 65. 7 figs.

In a study carried out at the Central Radiological Institute, Graz, of the changes in the peripheral circulation as a consequence of rheumatic disease a contrast medium was injected intra-arterially, and by taking serial radiographs it was possible to demonstrate peripheral vascular damage. In the normal hand the lateral and medial digital arteries are clearly defined, as is also the rich arterio-venous anastomatic network. But in cases of long-standing rheumatoid arthritis, for instance, narrowing or obliteration of the digital arteries at the level of the affected joints is usually found, while the terminal circulation is reduced owing to arterio-venous shunt, so that the venous return is retarded and varicosities appear. The author claims that by a modification of the radiological technique it is possible to demonstrate pathological changes in the peri-articular tissues. *David Preiskel.*

Action of Adenotriphosphatase on Shingles. (Action de l'adénotriphosphatase sur le zona.) BROUS, M. (1955). *Presse méd.*, **63**, 84.

Recurrent Rheumatism. (Rheumatismus palindromicus.) LEU, H. J. (1955). *Praxis*, **44**, 264. 28 refs.

Gold Salts in the Treatment of Infective Rheumatism. (Las sales de oro en la terapeutica de los reumatismos infecciosos.) COSTA BERTANI, G. (1955). *Rev. argent. Reum.*, **19**, 201.

Experimental Studies of the Mechanism of the Antiphlogistic Action of Phenylbutazone, Cortisone, and Salicylic Acid. (Experimentelle Untersuchungen über den Mechanismus der antiphlogistischen Wirkung von Butazolidin, Cortison und Salizylsaure.) SCHUMACHER, H. (1955). *Z. Rheumaforsch.*, **14**, 22. 1 fig., 6 refs.

Clinical and Therapeutic Aspects of Circulatory Disturbances in Rheumatic Disease. (Klinik und Therapie der peripheren Durchblutungsstörungen bei rheumatischen Erkrankungen.) BÖNI, A. (1955). *Z. Rheumaforsch.*, **14**, 13. 31 refs.

Peripheral Circulatory Disorders in Rheumatic Disease. (Über Probleme der peripheren Durchblutungsstörungen bei rheumatischen Erkrankungen.) FEYRTER, F. (1955). *Z. Rheumaforsch.*, **14**, 1. 43 refs.

Haematologic Observations in Short and Long-Term Treatment of Rheumatic Diseases with Phenylbutazone. HARRIS, S. B., and KLEIN, R. (1955). *N. Y. St. J. Med.*, **55**, 95. 4 refs.

Rheumatism and Work. (Reumatismo e lavoro.) MASTURZO, A. (1955). *Reumatismo*, 7, 85. 4 figs.

Mechanism and Therapeutic Role of Spinal Pumping in Arthritis. GHANEM, M. H. (1955). *Alexandria med. J.*, **1**, 114.

Calcinosis and Collagen Diseases. CONNER, S. K. (1955). *Ariz. Med.*, **12**, 277. 2 figs, 3 refs.

Relations between Thyroid Function and Rheumatic Tissue Reactions. (Über die Beziehungen zwischen Schilddrusenfunktion und rheumatischen Gewebsreaktionen.) KRUSKEMPER, H. L. (1955). *Z. Rheumaforsch.*, **14**, 180. 1 fig., 41 refs.

Phenylbutazone (Butazolidin) in the Treatment of Various Rheumatic Disorders. WORNOM, P. H., and SWINEFORD, O. (1955). *Va med. Mon.*, **82**, 176. 29 refs.

Metabolic Fate of Phenylbutazone (Butazolidin) in Man. BURNS, J. J., ROSE, R. K., GOODWIN, S., REICHENTHAL, J., HORNING, E. C., and BRODIE, B. B. (1955). *J. Pharmacol.*, **113**, 481. 2 figs, 9 refs.

Contribution to the Prophylaxis of Rheumatism. (Ein Beitrag zur Prophylaxe des Rheumatismus.) HILLER, E. (1955). *Z. Rheumaforsch.*, **14**, 116. 4 refs.

Methods of Estimating the Results of Treatment in Rheumatism. (Zur Methodik der Erfolgsneurteilung in der Rheumatherapie.) HALHUBER, M. J., HAUS, E., and INAMA, K. (1955). *Z. Rheumaforsch.*, **14**, 159. 11 refs.

Some Emotional Factors in Rheumatic Disease. BROWNING, J. S. (1955). *W. Va med. J.*, **51**, 103. 2 refs.

INDEX TO VOLUME XIV, 1955

* indicates that only the title of the article is given

ABD EL WAHAB, E. M., 446
Acid, acetyl salicylic: *see* Aspirin
——, amino, metabolism, hormones and, *103
——, ——, urinary, 186
——, ascorbic, plasma levels in arthritis, rheumatoid, and, *442
——, folic, in Felty's syndrome, 87
——, hippuric, 185
——, hyaluronic, in synovial fluid, 211
——, nicotinic, in diagnosis of arthritis, *105, *442
——, phenolic, action of, 444
——, polysaccharide, 288
——, salicylic, and gout, 444
——, uric, in serum, determination of, 405
Acta rheumatologica scandinavica, 303
ACTH, action of, 419
—— in Felty's syndrome, 87
—— in rheumatism, acute, heart damage after, 427
Acthar gel and diphenylamine reaction, 226
—— and erythrocyte sedimentation rate, 226
Acute rheumatism: *see* Rheumatism, acute
Adenosine mono- and di-nucleotide in arthritis, rheumatoid, *103
Adrenal function and 9-α-fluoro hydrocortisone acetate, 170
Adrenocortical hormones, biosynthesis and metabolism of, 419
Age and collagen content of human skin, 19
Agglutinins after antigenic inoculation, 243
Aldosterone in arthritis, rheumatoid, 101, 421
——, chemical structure of, 422
ALEXANDER, W. R. M.: *see* ROY, L. M. H., ALEXANDER, W. R. M., and DUTHIE, J. J. R.
American Council on Rheumatic Fever and Congenital Heart Disease, 425
AMERICAN RHEUMATISM ASSOCIATION: Experience with cortisone in the management of rheumatoid arthritis. Report of a co-operative study conducted by a committee of the American Rheumatism Association, 325
—— —— ——: First Interim Scientific Session, November, 1954, 93
—— —— ——: Proceedings of the Annual Meeting, 1955, 412
Amphetamine and pain sensation, 400
Amyloid, 288
Anaemia of arthritis, rheumatoid, 60, 63
——, normocytic hypochromic, incidence of, 84
Analogues of phenylbutazone, 434
ANDERSON, A. J., 301
Antibodies, incomplete, after antigenic inoculation, 243
Antihistamine and pain sensation, 400
Antistreptolysin-O, spectrophotometric determination of, *442
—— titre, measurement of, 407
APPLEBY, J. I., and NORYMBERSKI, J. K.: Urinary excretion of 17-hydroxy-20-oxosteroids in normal health and in rheumatoid arthritis, 172
Apresoline: *see* Hydralazine
Arteritis, cold-induced, *442
Arthritis, chronic, after recurrent rheumatic fever, 259
——, degenerative, therapy of, 440
——, ——, radiology of, *442
——, experimental, *105
——, ——, various types compared, 99
——, gouty, phenylbutazone in, 434
——, inflammatory, osteopathy in, 441
——, juvenile mono-articular, *442
——, Marie-Strümpell: *see* Spondylitis, ankylosing, 432
——, psoriatic, 202, 252
——, rheumatoid, 252
——, ——, adenosine mono- and di-nucleotide in, *103
——, ——, aldosterone in, 101, 421
——, ——, anaemia of, 60, 63
——, ——, aspirin in, 353
——, ——, blood tests in, 292
——, ——, —— volume in, 51
——, ——, cardiac changes in, 11, *303, 430
——, ——, in coal-miners, 150, 159
——, ——, corticotrophin-zinc hydroxide in, *104
——, ——, cortisone in, 325, 353
——, ——, differential diagnosis of, from lupus erythematosus disseminatus, 415
——, ——, diphenylamine reaction in, 226, 267
——, ——, dye-retention studies of, 51
——, ——, erythrocyte sedimentation rate in, 361
Arthritis, rheumatoid, fatalities and adverse reactions in, 302
——, ——, flocculation tests in, *103
——, ——, haemagglutination in, 96, 159, 431
——, ——, ——, and cortisone, 191
——, ——, haemoglobin levels in, 362
——, ——, heredity in, 154
——, ——, hormone therapy and anaemia in, 60
——, ——, hydrocortisone in, 232, 269
——, ——, and hyperadrenalism, 429
——, ——, incidence of, 446
——, ——, joint involvement in, 360
——, ——, laboratory procedures in, 404
——, ——, "L.E." phenomenon in, *442 *bis*
——, ——, liver function in, 162, 183
——, ——, metabolism in, *105
——, ——, metacortandracin in, 418, 421 *bis*
——, ——, niacin furfuryl test of, *442
——, ——, nicotinic acid in diagnosis of, *105, *442
——, ——, occupation and, 133, 150, 159
——, ——, paraffin-wax baths in, 278
——, ——, penicillin in, *442
——, ——, plasma ascorbic acid in, *442
——, ——, —— proteins in, *105
——, ——, plasmacytomatosis and, 271
——, ——, prognosis in, 133
——, ——, and psoriasis, 198, 440
——, ——, pulmonary disease and, 153, 159
——, ——, radiology of, 362
——, ——, and serum plasma, 195, 431
——, ——, —— protein/polysaccharide ratio in, *104
——, ——, social aspects of, 133
——, ——, sterno-clavicular joint in, 99
——, ——, steroid metabolism in, 183
——, ——, —— hormones in, *105
——, ——, —— —— and peripheral vessels in, 293
——, ——, synovial fluid in, 392, *442 *bis*
——, ——, urinary excretion of steroids in, 170, 172
——, ——, 9-α-fFa in, 101 *bis*, 170, 421
Arthropathy, cold-induced, *442
Arthroplasty, Ivalon, *442
ASBØE-HANSEN, G., 300
Aspirin compared with cortisone in arthritis, rheumatoid, 353
—— and diphenylamine reaction, 226
—— and erythrocyte sedimentation rate, 226
—— and pain sensation, 399
Assessment of disease activity, 136, 326, 358
ATHERDEN, S. M.: *see* ROY, L. M. H., WIGZELL, F. W., DEMERS, R., SINCLAIR, R. J. G., DUTHIE, J. J. R., ATHERDEN, S. M., and MARRIAN, G. F.
*AUERBACH, V. H., 103
AUSTEN, F. K., and CALKINS, E.: Serial studies of synovial fluid in evaluating intra-articular agents, 283
Autopsies of patients with arthritis and heart diseases, 12
*AVERILL, K. H., 442

BADGLEY, C. E., 438
BADIN, J., 96
BAKER, D. M.: Changes in the corium and subcutaneous tissues as a cause of rheumatic pain, 385
BALL, J.: Differential agglutination test in rheumatoid arthritis complicated by pneumoconiosis, 159
BALLABIO, C. B.: *see* VILLA, L., BALLABIO, C. B., and SALA, G.
BASSIOUNI, M.: Studies of the acid polysaccharide of the white cells in rheumatic and other diseases, showing its similarity to the acid polysaccharide of amyloid, 288
BATEMAN, J. E., 435, 436
*BATTERMAN, R. C., 442
BAUER, W., 416, 418, 419
BAYLES, T. B., 95, 102, 431
BEATTIE, J. W.: *see* WOODMANSEY, A., and BEATTIE, J. W.
——, and WOODMANSEY, A.: Radiation pain thresholds in relation to skin temperatures, 397
BEELAR, V. P., 100
*BELLER, M. L., 443
*BENSLEY, S. H., 105
BERENSON, G. S., 425
BERGENSTAL, D. M., 94, *103, *442

Berkson's fallacy, 349
BIEN, E., 98, 99
——, and ZUCKER, M.: Uricolysis in normal and gouty individuals, 409
Bilirubin, measurement of, 65
BLACK, R. L., 418, *442
BLAIR, A., 433
*BLAIR, J. R., 442
*BLAIS, J. A., 303
Blood disease and Felty's syndrome, 84
——, hyaluronidase inhibitor of, 425
—— pressure and Heberden's nodes, 7
—— —— of nephrectomized rats, 74
—— protein disorder and arthritis, rheumatoid, 271
—— tests in rheumatism, acute, 288
—— transfusion in Felty's syndrome, 85
—— volume measurement in arthritis, rheumatoid, 51
BLUMBERG, B., *103, 432, 433, 445
BOCKING, D., 99
Body weight of nephrectomized rats, 74
Bone density, carcinoma and, 383
—— erosion in arthritis, rheumatoid, 364
——, fluoride concentrations in, 382
—— marrow in arthritis, rheumatoid, 273
—— —— in Felty's syndrome, 85
*BOHROD, M. G., 443
BOLAND, E. W.: Oral hydrocortisone therapy in rheumatoid arthritis; an appraisal of general results of prolonged administration, 232
——: 101, 102, 421, 424
BOLLET, A. J., 102, 417, 418, *442
BOOK REVIEWS:
ABBOTT, M. E.: Atlas of Congenital Cardiac Disease, 1954, 92
Acta rheumatologica scandinavica, 303
BOHMAN, F.: Gold Treatment of Rheumatoid Arthritis. *Acta genetica et statistica medica*, Suppl. 3, vol. 5, 1954, 299
COPEMAN, W. S. C. (Editor): Textbook of the Rheumatic Diseases, 2nd edition, 1955, 92
——, and MASON, R. M.: Rheumatism, 1954, 92
COSTE, F., and 29 other contributors: Le rhumatisme. Études cliniques, biologiques, et thérapeutiques (3e série), 1954, 298
DEBEYRE, J., and DOLIVEUX, P.: Les arthroplasties de la hanche, 1955, 299
DEBRÉ, R., and SOULIÉ, P.: La maladie de Bouillaud. Ses complications cardiaques et son traitement, 1955, 299
FENZ, E.: Behandlung rheumatologischer Erkrankungen durch Anästhesie, 1955, 298
LIÈVRE, J. A.: Comment traiter la sciatique, 1954, 92
LUCHERINI, T., and CERVINI, C.: La spondilite anchilosante, 1955, 443
ROMANUS, R., and YDÉN, S.: Pelvo-spondylitis ossificans, 1955, 298
BOOTS, R. H., 97
Brazilian League against Rheumatism, 106, 212
BRIEN, F. S., 99
BRODIE, B. B., 434
Bromsulphophthalein retention, 65
—— test, 186
BROWN, E. M., 439
*BROWN, H., 442
BROWN, P., 96
BROWN, T. McP., 439
Brucella abortus, immunization with, 243
*BRUCE-ROBERTSON, A., 105
BRUGSCH, H. G., *104, *442
BUCKLEY, Dr. Charles William. Obituary, 213
BUNIM, J. J., 96, 102, 103, 415, 417, 418, 420, 423, 428, 429, 431, *442
BURNS, J. J., 434, 435
Butazolidin: *see* Phenylbutazone
*BYWATERS, E. G. L., 212

Calcification, paraplegic, para-articular, 176
—— of vertebral column, 378
Calcinosis, chelation in, 445
CALKINS, E., 419
——: *see* AUSTEN, F. K., and CALKINS, E.
*CAMERON, G., 442
Canada, First Conference on Research in Rheumatic Disease, 1955, 105
Canadian Rheumatism Association Annual Meeting, 1955, 303
Caplan's syndrome, 150, 159
Carcinoma, metastatic, bone density in, 383
Carditis and arthritis, rheumatoid, 11, *303
——, rheumatic, 252
——, ——, cortisone in, 427
——, ——, hydrocortisone in, 427
—— and spondylitis, *303, 446
CARLIN, W., 441
*CARTER, A., 303
Cartilage mucoprotein, 95 *bis*, 412
——, radioactive sulphur uptake of, hydrocortisone and, 94
Case records in study of chronic disease, 337
CECCHI, E., and FERRARIS, F.: Serum diphenylamine reaction in rheumatoid arthritis, 267
CECIL, R. L., 445
CHATELIN, N. H., 413
Chelation in calcinosis, 445
—— in sclerodactylia, 445
—— in scleroderma, 445
CHITI, E.: *see* GALLI, T., and CHITI, E.
Chorea, blood tests in, 288
——, Sydenham's, *443
CLARK, Dr., 101
CLARK, W. S., 430, 431
Coal-miners, arthritis in, 150, 159
*COBB, S., 442
*COBEY, M. C., 442
Codeine and diphenylamine reaction, 226
—— and erythrocyte sedimentation rate, 226
COGGESHALL, H. C., 97
Colcemide, intravenous, in gout, *442
Collagen disease, hypersensitivity and, *105
—— formation and mucoproteins, 95
—— in human skin, electron microscope studies, 19
—— metabolism, 238
——, neutral salt-soluble, 446
COLLINS, D. H., 302
Commissurotomy, mitral, and Group-A streptococcal infection, 425
——, ——, selection of patients for, *303
Congo red, plasma retention of, 52
CONTRERAS, V., 444
COPE, C. L., and SEWELL, C. E.: The presence of natural hydrocortisone in synovial fluid, 392
Corium, changes in, and rheumatic pain (panniculosis), 385
Corticosteroids, enzymatic metabolism of, 100
—— in normal and arthritic blood before and after ACTH, *105
Cortisone in arthritis, rheumatoid, 325
——, ——, ——, compared with aspirin, 353
—— in carditis, rheumatic, 427
——, chemical structure of, 422
——, co-operative study of therapy, 326
——, diabetogenic properties of, *443
—— and haemagglutination in arthritis, rheumatoid, 191
—— metabolism, 421
—— —— compared with prednisone, 419
—— in panniculosis, 390
—— and peripheral vasculature, 293
—— and pneumonia, 211
—— and regeneration of limbs, 93
—— in rheumatism, acute, heart damage after, 427
——, side-effects of, *442
—— therapy, survey of American Rheumatism Association co-operative study, 337
Cortisol: *see* Hydrocortisone
C-Reactive Protein: *see* Protein, C-Reactive
CUDKOWICZ, L.: *see* ELLMAN, P., CUDKOWICZ, L., and ELWOOD, J. S.
*CURTISS, P. H., 442

Δ^1-Cortisone, 446
Δ^1-Dehydrocortisone, chemical structure of, 422
Δ^1-Dehydrohydrocortisone, chemical structure of, 422
*DARRACH, M., 105
*DAUPHINÉE, J. A., 105
DAVIDSON, E. A., 96
DE COEK, N.: *see* FEARNLEY, G. R., PIRKIS, J., DE COEK, N., LACKNER, R., and MEANOCK, R. I.
Deformities, arthritic, of the hand, 435
*DEMERS, R., 303
——: *see* ROY, L. M. H., WIGZELL, F. W., DEMERS, R., SINCLAIR, R. J. G., DUTHIE, J. J. R., ATHERDEN, S. M., and MARRIAN, G. F.
DENKO, C. W., 94, 95, *103, *442
Dermatomyositis, musculoskeletal manifestations of, 413
Desoxycorticosterone acetate, effect of, 73
—— and ascorbic acid and peripheral vasculature, 294
——, chemical structure of, 422
Diagnosis in rheumatic disease, *303
DINGLE, J. T.: *see* THOMAS, D. P. PAGE, and DINGLE, J. T. M.
Diphenylamine reaction in arthritis, rheumatoid, 226, 267
—— —— in spondylitis, ankylosing, 269
Disk, intravertebral, degeneration of, 301, 302
——, ——, hydrocortisone injections into, 439
Diuretics, mercurial, and plasma phenylbutazone, *442
DIXON, A. ST. JOHN, RAMCHARAN, S., and ROPES, M. W.: Rheumatoid arthritis: dye retention studies and comparison of dye and radioactively labelled red cell methods for measurement of blood volume, 51
DOCA: *see* Desoxycorticosterone acetate
DOLAN, M. A., 425
DORDICK, J. R., 445
DORFMAN, A., 425

DORFMAN, R. I., 419, 423, 424
Dublin Rheumatism Association Annual Report, 1952-53, 106
DUFF, I. F., 413, 432, *442
*DURIVAGE, J., 303
*DUSSAULT, R., 303
DUTHIE, J. J. R., 300
——: *see* ROY, L. M. H., ALEXANDER, W. R. M., and DUTHIE, J. J. R.
——: *see* ROY, L. M. H., WIGZELL, F. W., DEMERS, R., SINCLAIR, R. J. G., DUTHIE, J. J. R., ATHERDEN, S. M., and MARRIAN, G. F.
——, THOMPSON, M., WEIR, M. M., and FLETCHER, W. BELL: Medical and social aspects of the treatment of rheumatoid arthritis, with special reference to factors affecting prognosis, 133
Dye-retention in blood in arthritis, rheumatoid, 51
Dysprotidaemia in joint disease, 271

*EASLING, H., 443
EGELIUS, N., GÖHLE, O., JONSSON, E., and WAHLGREN, F.: Cardiac changes in rheumatoid arthritis, 11
Elastin metabolism, 238
Electrocardiograph in arthritis with heart disease, 14
Electrocortin: *see* Aldosterone
Electron microscope studies of human skin collagen, 19
Electrophoresis, 273, 290
—— of plasma proteins in arthritis, rheumatoid, 187, 193
—— of synovial fluid, 93
*ELLIOTT, A. J., 303
ELLMAN, P., CUDKOWICZ, L., and ELWOOD, J. S.: Therapy of "Felty's syndrome", 84
ELWOOD, J. S.: *see* ELLMAN, P., CUDKOWICZ, L., and ELWOOD, J. S.
EMPIRE RHEUMATISM COUNCIL: Multi-centre controlled trial comparing cortisone acetate and acetyl salicylic acid in the long-term treatment of rheumatoid arthritis. Results up to one year, 353
—— —— ——: Short report of Cortisone/Aspirin trial, 302
—— —— ——: Eighteenth annual report, 1954, 208
Enzyme concentrations in serum in rheumatism, acute, 425
—— metabolism of corticosteroids, 100
Erythrocyte sedimentation rate in arthritis, rheumatoid, 361
—— —— —— and diphenylamine reaction, 226, 267
—— —— —— in spondylitis, ankylosing, 269
—— —— —— technique, 404
European League against Rheumatism: *see* Ligue Européenne contre le Rhumatisme
Evaluation of therapy, *303
Evans' blue, plasma retention of, 51
Excretion, urinary, of iron, 67
——, ——, of steroids, 170, 172
Eyes in spondylitis, 80

Familial incidence of Heberden's nodes, 2
FARROW, I. J.: *see* LEFKOVITS, A. M., and FARROW, I. J.
FEARNLEY, G. R., PIRKIS, J., DE COEK, N., LACKNER, R., and MEANOCK, R. I.: Diphenylamine reaction in rheumatoid arthritis, 226
FEFFER, H. L., 439
FELDMAN, H. A., 426, 428, *442 *bis*
Felty's syndrome, therapy of, 84
FERRARIS, F.: *see* CECCHI, E., and FERRARIS, F.
Fibromyalgia, *104
Fibromyopathy, neurogenic, ossifying, 176
Finger joints, osteo-arthritis of, 1
FISCHEL, E. E., 100, 427
*FLETCHER, A. A., 303
FLETCHER, W. BELL: *see* DUTHIE, J. J. R., THOMPSON, M., WEIR, M. M., and FLETCHER, W. BELL
Flocculation tests, *103
—— —— in spondylitis, 83
Fluorosis, crippling, 378
FORSHAM, P., 416
*FRANCOEUR, L., 303
FRANK, C. W., 100
*FRERICKS, C. T., 442
FREYBERG, R. H., 415, 441, *443
FRIBERG, S., 301
FRIED, J., 420, 423, 424
Frostbite, experimental, *442
Fructose tolerance, 186
Functional capacity of arthritis patients, 333, 359

GALLI, T., and CHITI, E.: Rheumatoid arthritis and plasmacytomatosis, 271
GARDNER, D. E.: *see* STEINBERG, C. L., GARDNER, D. E., SMITH, F. A., and HODGE, H. C.
GERMUTH, F. G., 413
*GILLEN, A. L., 442
GILLILAND, I. C., 446
GLEASON, I. O., 99
Glomerulonephritis in kidney biopsies, 373, 413
GLYNN, L. E., 300
GÖHLE, O.: *see* EGELIUS, N., GÖHLE, O., JONSSON, E., and WAHLGREN, F.
GORDON, A. S., 436
*GORNALL, A. G., 105
Gout, 252
——, colcemide in, *442
——, phenylbutazone in, 434 *bis*
——, social studies of, *442
—— in South Africa, 302
——, urate excretion in, salicylate and, 444
——, —— synthesis in, 433
——, uricolysis in, 98, 409
*GRAHAM, D. C., 303 *bis*
*GRAHAM, W., 303
GRIBBLE, M. DE G.: Rheumatoid arthritis and psoriasis, 198
GRIBETZ, H. J., 412
Growth hormone and thyroidectomized rats, 73
*GULLAR, E. J., 442
GUTMAN, A. B., 434, 444
G 2567, 434
G 25903, 434
G 13838, 434
G 28231, 434
G 27202, 434

Haemagglutination reaction in arthritis, rheumatoid, 96, 431
—— —— —— with pneumoconiosis, 159
——, cold precipitable factor, 191
—— titre, measurement of, 406
Haemoglobin levels in arthritis, rheumatoid, 362
*HAGEMANN, P. O., 442
*HAHN, J. W., 103
Halogenated analogues of steroid hormones, 420
Hand, arthritic deformities of, 435
——, rehabilitation of, 439
*HARGIS, B., 103
HARRIS, R.: A simple posture meter, 90
——, and MILLARD, J. B.: Paraffin-wax baths in the treatment of rheumatoid arthritis, 278
HARRIS, S. B., 445
*HARRIS, W. R., 303
HART, F. DUDLEY: Ankylosing spondylitis: a review of 184 cases, 77
HARTUNG, E. F., and MAHOOD, M. E.: Routine laboratory procedures in arthritis and related disorders, 404
Havana, University of, Summer School Rheumatology Course, 303
HAYDU, G. G., *103, *442
HEADLEY, N. E., 101
Heart changes in arthritis, rheumatoid, 11, 430
—— damage after rheumatism, acute, 427
Heberden Oration, 1954, 1
—— ——, 1955. Cancellation, 302
Heberden Round, 1955, 212
Heberden Society:
Clinical meeting, February 18, 1955, 105, 211
—— ——, July, 1955, 301
Annual General Meeting, November, 1955, 446
Heberden's nodes, clinical description and differential diagnosis, 1
*HELLBAUM, A. A., 104
Heller-Rose test, 406
HENCH, P. S., 101, 416, 421
Heredity in arthritis, rheumatoid, 154
*HESS, E., 212
HILL, R., 97
Hip, reconstruction of, in arthritis, 438
Histology of lupus nephritis, 371, 413
HODGE, H. C.: *see* STEINBERG, C. L., GARDNER, D. E., SMITH, F. A., and HODGE, H. C.
HOFFMAN, P., 96
HOLBROOK, W. P., 438
HOLLANDER, J. L., 102, *442
HOLLEY, H. L., 93
HORMELL, R. S., 436
Hormone, growth, 73
—— therapy and blood volume in arthritis, rheumatoid, 60
——, thyrotrophic, 73
*HOULI, J., 103
——: Artrite reumatoide, 1953, 300
HOWELL, D. S., 429, 430, 445
HUFFMAN, E. R., 97, 434
HUSSAR, A. E., 442
*Hydralazine, *303
——, syndromes of collagen disease caused by, 99
Hydrocortisone in arthritis, rheumatoid, 232, 269
—— in carditis, rheumatic, 427
——, chemical structure of, 422
—— diabetogenic properties of, *443

Hydrocortisone and diphenylamine reaction, 269
—— and erythrocyte sedimentation rate, 269
——, estimation of, 393
—— and intervertebral disks, 439
——, intra-articular, 284
——, natural, in synovial fluid, 392
—— in osteo-arthritis, *442
——, pharmacology and metabolism of, 421
—— and radioactive sulphur uptake of cartilage, 94
——, synthesis rate of, 421
Hyperadrenalism and arthritis, rheumatoid, 429
Hypercortisonism, chronic, recognition and treatment of, 416
Hypersensitivity and serum sickness, 413
Hyperuricaemia in gout, 407
Hypospray in intra-articular injection, 444
Hypotension as cause of collagen disease syndromes, 99
Hypoxaemia test in arthritis with heart disease, 14

Immunization in rheumatism, acute, 243
Inflammation, anaphylactoid, *105
Inheritance of Heberden's nodes, 3
Inoculation, antigenic, and agglutinins and incomplete antibodies, 243
Intra-articular therapy evaluated by synovial fluid tests, 283
Iritis in spondylitis, 80
Iron in Felty's syndrome, 85
—— metabolism, 63
——, plasma levels of, in arthritis, rheumatoid, 64
——, saccharated oxide of, in arthritis, rheumatoid, 64
IRVINE, J. H., *104, *442
ISDALE, I., 446
ISHMAEL, W. K., *104, 415, 416, 440, *442
ISSELBACHER, K. J., 100
Ivalon in knee arthroplasty, *442

JACKSON, D. S., 446
JACOBS, J. H., 211
*JASMIN, G., 105
JESSAR, R. A., 439
*JIVOFF, L., 442
*JOHNSTON, L. G., 105
Joint disease and dysprotidaemia, 271
—— dynamics (film), 441
—— involvement in arthritis, rheumatoid, 360
——, sterno clavicular, in arthritis, rheumatoid, 99
JONSSON, E.: *see* EGELIUS, N., GÖHLE, O., JONSSON, E., and WAHLGREN, F.

KAMMERER, W. H., 93, 96, 97, 418, 445
KANTOR, T. G., 95, 96
KAPLAN, L., 430
*KARK, R. M., 442
——: *see* MUEHRCKE, R. C., KARK, R. M., PIRANI, C. L., POLLAK, V. E., and STECK, I. E.
KEECH, M. E.: Human skin collagen from different age groups before and after collagenase digestion; an electron microscopic study, 19
*KEITH, J. D., 105
KELLGREN, J. H., 446
KENYON, A. T., 94
KEY, A. J., 438, 439
KLEIN, R., 445
*KLING, D. H., 442 *bis*
KLOOS, G., 441
Knee arthroplasty, Ivalon, *442
——, punch biopsy of, *443
——, reconstruction of, in arthritis, 437
Kidney: histology of lupus nephritis, 371, 413
KUHNS, J. G., 433, 440
*KULKA, J. P., 442
KUTTNER, A., 427
KUZELL, W. C., 98, 100, *442

LACKNER, R.: *see* FEARNLEY, G. R., PIRKIS, J., DE COEK, N., LACKNER, R., and MEANOCK, R. I.
LA DUE, J. S., 425
*LAMPE, I., 442
LANSBURY, J., 99, 100
LAWRENCE, J. S., 302, 446
LEFKOVITS, A. M., and FARROW, I. J.: The liver in rheumatoid arthritis, 162
*LEIFER, P., 442
Leucocytes and mucoprotein viscosity, 412
Leucopenia in Felty's syndrome, 85
LEVIN, M. H., 430, 431, *443
*LEVINE, M. G., 442 *bis*
*LEWIS-FANING, E., 212
LIGUE EUROPÉENNE CONTRE LE RHUMATISME: Third European Rheumatology Congress, 1955, Programme, 104
—— —— ——, Report, 300
LINKER, A., 96
Liver in arthritis, rheumatoid, 162, 183
LOCKEY, E., 301
LOCKIE, L. M., 434
*LONG, L., 303
Lord Horder, Obituary, 225
LOSPALLUTO, J., 412
Lung, nodular fibrosis of, and arthritis, rheumatoid, 151, 159
Lupus erythematosus, 252
—— —— cell reaction, *105
—— —— cells, test for, 407
—— ——, disseminated, musculoskeletal manifestations of, 413
—— ——, ——, diagnosis of, 415
—— ——, ——, metacortandracin in, *443
——, ——, morphology and specificity of, 414
—— —— phenomenon in arthritis, rheumatoid, *442 *bis*
—— ——, systemic, metacortandracin in, 417
—— ——, ——, simulated acute abdomen in, *442
—— nephritis, histological and clinical evolution of, 371, 413
LYNCH, W. F., 425

MCCOY, F. W., 415, 416, *443
*MCDONALD, G. A., 303
MCEWEN, C., 96, 97, 100, 429, 437
*MACKENZIE, K. R., 105
MACLAGAN, N. F.: Ankylosing spondylitis—Laboratory investigations, 83
MAHOOD, M. E.: *see* HARTUNG, E. F., and MAHOOD, M. E.
MAINLAND, D.: Use of case records in the study of therapy and other features in chronic disease. I. Planning the survey, 337
Males, arthritis in, 150
*MANDEL, L., 303
MANNER, H. W., 93
MARCUS, S., 430, *443
MARKHAM, R. L., 212
MARKOWITZ, M., 427, 429
MARRIAN, G. F.: *see* ROY, L. M. H., WIGZELL, F. W., DEMERS, R., SINCLAIR, R. J. G., DUTHIE, J. J. R., ATHERDEN, S. M., and MARRIAN, G. F.
MASSELL, B. F., 427
MATHEWS, M. B., 425
MEANOCK, R. I.: *see* FEARNLEY, G. R., PIRKIS, DE COEK, N., LACKNER, R., and MEANOCK, R. I.
*MEIHAUS, J. E., 443
Menopause and Heberden's nodes, 6
——, skin changes and rheumatic pains in, 386
*MERCHANT, W. R., 442
Metabolism of connective tissue, 238
Metacortandracin, 102, 251, 445 *bis*, *303 *bis*
—— in arthritis, rheumatoid, 301, 418, 421 *bis*
——, chemical structure of, 422
——, "diabetogenic" properties of, *443
—— in lupus erythematosus, 417, *443
——, metabolism of, 419, 421
—— in rheumatism, acute, *442
——, side-effects of, 445
Metacortandralone, 102
——, chemical structure of, 422
Meticortelone: *see* Metacortandralone
Meticorten: *see* Metacortandracin
MEYER, K., 94, 96, *103
MIALL, W. E.: Rheumatoid arthritis in males; an epidemiological study of a Welsh mining community, 150
MIKKELSEN, W. M., 413
MILLARD, J. B.: *see* HARRIS, R., and MILLARD, J. B.
*MOORE, R., 442
*MORE, R. N., 105
Morphine sulphate and pain sensation, 400
*MORROW, J. D., 303
*MOVAT, H., 105
Mucopolysaccharides, 95, 96
——, metabolism of, 241
Mucoprotein, 95 *bis*
—— estimation in arthritis, rheumatoid, 301
—— from cartilage, viscosity of, 412
*MUEHRCKE, R. C., 442
——, KARK, R. M., PIRANI, C. L., POLLAK, V. E., and STECK, I. E.: Histological and clinical evolution of lupus nephritis, 371, 413

*NAUGLER, W. E., 442
Nephrectomy, experimental, 73
Neuro-arthropathy, 176
*NEUSTADT, D. H., 104
NEWMAN, J. K., 425
NEWNS, G. R., 301

New York Rheumatism Association, 444
Niacin furfuryl test in arthritis, rheumatoid, *442
Nodules, cortisone and, 330
Norymberski, J. K.: *see* Appleby, J. I., and Norymberski, J. K.
Nydick, I., 425, 426

Obesity and Heberden's nodes, 7
Obituary:
C. W. Buckley, 213
Lord Horder, 225
Oestrogen (Oestradiol) and peripheral vasculature, 294
—— in treatment of panniculosis, 390
Ogryzlo, M. A., *105, *303, 414, 415
Orbison, J. L., 431
Orthopaedic surgery, 437, 438
Ossification para-articular, 176
Osteo-arthritis, 252
—— of cervical spine, 440
—— of finger joints, 1
——, hydrocortisone in, *442
——, incidence of, 446
Osteogenesis imperfecta tarda, *443
Osteopathy, resorptive, in arthritis, 441
*Owens, J. N., 442

Paget's disease, joint changes in, *443
Pain, rheumatic, with changes in corium and subcutaneous tissue (panniculosis), 385
—— in spinal disease, *442 *bis*
—— threshold and skin temperature, 397
I Pan-American Congress of Rheumatology, 1955, 106, 212
Panniculosis, 385, 391
Paraffin-wax baths in arthritis, rheumatoid, 278
Para-osteo-arthropathy, 176
Passarelli, E. W., 440
Paton, B. C., 434
Patterson, J., 430, *443
Patterson, M., 415
Payne, R. W., *104, *442
*Pearce, R. H., 105
*Pease, G. L., 442
Pechet, M. M., 102
Pedigree of Heberden's nodes, 8
Penicillin prophylaxis in arthritis, rheumatoid, *442
Periarteritis nodosa, hypersensitivity and, 413
—— ——, metacortandracin in, *443
—— ——, musculoskeletal manifestations of, 413
Periostitis, cold-induced, *442
Peterson, R. E., 421
Phenylbutazone, *103, *104 *bis*, 444
——, analogues of, 434
—— in arthritis, gouty, 434
—— and diphenylamine reaction, 226, 269
—— and erythrocyte sedimentation rate, 226, 267
—— in panniculosis, 390
——, plasma levels of, and mercurial diuretics, *442
——, renal effects of, 434
——, side-effects of, *442
——, uricosuric effect of, 97
Physiotherapy in panniculosis, 390
*Pierik, M. G., 442
Pigman, W., 93, 95, 96
Pilkington, T. L., 301
Pirani, C. L.: *see* Muehrcke, R. C., Kark, R. M., Pirani, C. L., Pollak, V. E., and Steck, I. E.
Pirkis, J.: *see* Fearnley, G. R., Pirkis, J., de Coek, N., Lackner, R., and Meanock, R. I.
Planning a statistical study of case-records, 337, 353
Plasma bilirubin, 185
—— cholesterol, 186
—— iron, 66
—— proteins, 65, *105, 186
—— urate in gout, 408
—— volume, measurement of, 54
Plasmacytomatosis and arthritis, rheumatoid, 271
Plasmin activity in arthritis, rheumatoid, 195
Platt, D., 93, 94
Plotz, C., 418, 445
Pneumoconiosis and arthritis, rheumatoid, 159
Pneumonia, masked, during cortisone therapy, 211
"Poker" back, 378
*Pollak, V. E., 442
——: *see* Muehrcke, R. C., Kark, R. M., Pirani, C. L., Pollak, V. E., and Steck, I. E.
Polley, H. F., 101, 416, 421, *442
*Popovici, A., 442
Post, A., 441
Posture meter, 90
Potter, T. A., 438
Prednisolone: *see* Metacortandralone
Prednisone: *see* Metacortandracin
Pregnanediol excretion, 189
Pregnenolone, chemical structure of, 422
Preston, R. L., 437, 438
Progesterone and peripheral vasculature, 294
—— and pregnanediol excretion, 189
Prognosis, 300
—— in arthritis, rheumatoid, *303
Protein, C-Reactive, detection of, 405
——, plasma, in spondylitis, 83
Psoriasis, arthritis and, 198, 446
——, cortisone and, 330
Psychosis and arthritis, rheumatoid, 301

Radioactively labelled red cells in blood volume measurement, 51
—— sulphur uptake of cartilage, hydrocortisone and, 94
Radiology of arthritis, rheumatoid, 362
—— of calcification, 178
—— of chest in arthritis, rheumatoid, 150, 159
—— of fluorosis, 380
—— of Heberden's nodes, 7
—— of spinal disease, *442
—— of spondylitis, 80
—— of ——, ankylosing, 381
Radiotherapy in spondylitis, ankylosing, *442
Ramcharan, S.: *see* Dixon, A. St. John, Ramcharan, S., and Ropes, M. W.
Rawls, W. B., 444
Record form for survey of clinical response to therapy, 327, 342, 356
Rehabilitation, 301
—— of the hand, 439
Reiter's syndrome, diphenylamine reaction in, 227
Rejholec, V.: *see* Wagner, V., and Rejholec, V.
Renal function in lupus nephritis, 376, 413
Reznick, L., 419
Rheumatic fever: *see* Rheumatism, acute
Rheumatism, acute, 252
——, ——, antigenic inoculations in, 243
——, ——, blood tests in, 288
——, ——, chronic arthritis after, 259
——, ——, heart damage in, after steroid therapy, 427
——, ——, hormones and salicylates in, 100
——, ——, immunization in, 243
——, ——, metacortandracin in, *442
——, ——, phenylbutazone in, *104
——, ——, serum concentrations of glutamic oxalacetic transaminase in, 425, 446
——, ——, treatment of, *105
——, systemic, and nodular vasculitis, 431
Rheumatoid arthritis: *see* Arthritis, rheumatoid
*Richardson, A. T., 212
*Robinson, H. S., 303
*Robinson, W. D., 442
Rodnan, G. P., 414, 418, *442
Rogers, F. B., 99
*Roodenburg, A. I., 443
Ropes, M. W., 94, *442
——: *see* Dixon, A. St. John, Ramcharan, S., and Ropes, M. W.
Rose, F. Clifford, 211
Rose test, 406
*Rosen, P. S., 303
*Rosenbaum, J. R., 442
Rosenberg, E. F., 430
Roy, L. M. H., Alexander, W. R. M., and Duthie, J. J. R.: Nature of anaemia in rheumatoid arthritis. I. Metabolism of iron, 63
——, Wigzell, F. W., Demers, R., Sinclair, R. J. G., Duthie, J. J. R., Atherden, S. M., and Marrian, G. F.: Liver function in relation to possible abnormalities of steroid metabolism in rheumatoid arthritis, 183
Roy, S. B., 427, 429
*Rubin, H. S., 104
Rudd, E., 441
*Ruhman, W., 303
Ruml, D., *103, *442

Sala, G.: *see* Villa, L., Ballabio, C. B., and Sala, G.
Salgado, E.: Action of hypophyseal growth and thyrotrophic hormones in thyroidectomized rats, 73
Salt and sodium hyaluronate, *103
*Schaffarzick, R. W., 442
*Schaffner, F., 104
*Schatzki, R., 442
*Scherbel, A. L., 104
Schlossmann, K.: *see* Svartz, N., and Schlossmann, K.
Schmid, F., 444
Schubert, M., 95 *bis*, 412

SCHWEDEL, J. B., 425
Sclerodactylia, chelation in, 445
Scleroderma, 252
——, chelation in, 445
——, diffuse, metacortandracin in, *442
——, ——, musculoskeletal manifestations of, 413
SEGAL, S., 417, 418
Selection of patients in a statistical study, 337, 354
*SELYE, H., 105
Serology of arthritis, rheumatoid, 405
—— of spondylitis, 80
Serum antiplasmin and plasmin in arthritis, rheumatoid, 195
—— cholinesterase, 186
—— iron, 66
—— mucoproteins, electrophoresis of, 212
—— phosphatase, 185
—— protein/polysaccharide ratio in arthritis, rheumatoid, *104
—— —— in rheumatism, acute, 446
—— sickness, hypersensitivity and, 413
—— uric acid determination, 405
SEWELL, C. E.: *see* COPE, C. L., and SEWELL, C. E.
Sex ratio of Heberden's nodes, 3
SHARP, J., 446
SHATTON, J., 95
*SHETLAR, M. R., 104
SHORT, C. L., 100
Shoulder, painful, *303
SHULMAN, L. E., 414
Side-effects, 252
—— on aspirin therapy, 328, 357
—— on cortisone therapy, 357
SIGLER, J. W., 102
SILVER, M., 441
SINCLAIR, R. J. G.: *see* ROY, L. M. H., WIGZELL, F. W., DEMERS, R., SINCLAIR, R. J. G., DUTHIE, J. J. R., ATHERDEN, S. M., and MARRIAN, G. F.
Sjögren's syndrome, *303
Skin changes and rheumatic pain (panniculosis), 386
—— collagen, electron microscope studies, 19
——, temperature of, and pain sensation, 397
SLACK, H. G. B.: Short review of connective tissue metabolism, 238
SLOCUMB, C. H., 101, 415, 416, 421, 424, *442
SMITH, F. A.: *see* STEINBERG, C. L., GARDNER, D. E., SMITH, F. A., and HODGE, H. C.
SMYTH, C. J., 97, 103, 434
SMYTHE, H., *303, 431
Social factors in prognosis, *303
—— studies of ankylosing spondylitis, *443
—— —— of gout, *442
Società Italiana di Reumatologia. 3rd Rome Rheumatology Day, 1955, 106
SOCIETIES:
American Rheumatism Association, 93, 325, 412
Brazilian Rheumatism Society, 106, 212
Canadian Arthritis and Rheumatism Society, 105
Canadian Rheumatism Association, 303
Cuban League against Rheumatism, 303
Dublin Rheumatism Association, 106
Empire Rheumatism Council, 208, 302
Heberden Society, 1, 105, 211, 301, 446
Ligue Européenne, 104, 300
Pan-American League against Rheumatism, 106, 212
Società Italiana di Reumatologia, 106
Sodium chromate ^{51}Cr in measuring blood volume, 54
—— hyaluronate, salt and, *103
SOKOLOFF, L., 99
SOUGIN-MIBASHAN, R., 302
Spine, cervical, osteo-arthritis of, 440
——, measurement of movement of, 78
Splenectomy in Felty's syndrome, 85
Spondylitis, ankylosing (rheumatoid), 378
——, ——, age at onset, 77
——, ——, blood volume in, 51
——, ——, cardiac involvement in, *303
——, ——, diphenylamine reaction in, 269
——, ——, laboratory investigations in, 83
——, ——, natural history of, 432
——, ——, radiotherapy in, *442
——, ——, sex ratio in, 77
——, ——, social study of, *443
——, ——, symptomatology, 77
——, and carditis, rheumatoid, *104, *303, 446
Spondylo-arthritis, 252
Spondylometer, 78
STECHER, R. M.: Heberden Oration: Heberden's nodes. A clinical description of osteo-arthritis of the finger joints, 1
*STECK, I. E., 442
——: *see* MUEHRCKE, R. C., KARK, R. M., PIRANI, C. L., POLLAK, V. E., and STECK, I. E.
STEELE, J. M., 434
*STEIN, I., 443
STEINBERG, C. L., *104, 414, 417, *443
——, GARDNER, D. E., SMITH, F. A., and HODGE, H. C.: Comparison of rheumatoid (ankylosing) spondylitis and crippling fluorosis, 378
STEINBROCKER, O., 98, *104, 441
Steroid hormones, *105 *ter*, 419, 420
—— metabolism and liver function in arthritis, rheumatoid, 183
—— in synovial fluid, 394
Sterno-clavicular joint in arthritis, rheumatoid, 99
STEVENSON, C., 419, *443
STH: *see* Growth hormone
Still-Chauffard disease, 252
STOLLERMAN, G. H., 425 *bis*, *443
STOREY, G., and TEGNER, W. S.: Paraplegic para-articular calcification, 176
*STRANGE, D. A., 443
Streptococcal infection, Group A, and mitral commissurotomy, 425
—— —— and Sydenham's chorea, *443
Streptococcus, Group A, haemolytic, Type 6, *103
Surgery in arthritis, rheumatoid, *303
——, orthopaedic, 435, 437, 438
SVARTZ, N., and SCHLOSSMANN, K.: Cold precipitable haemagglutinating factor in serum from patients with rheumatoid arthritis, 191
SWANSON, J. N., 98, *303 *bis*, 435
*SWANSON, N., 105
*SWEZEY, R. L., 443
SWIFT, —, 441
Switzerland, arthritis in, 300
—— social medicine in, 300
Sydenham's chorea and streptococcal infection, *443
Symptoms, rheumatic, distribution of, *442
Synovial fluid, analysis of, 393, *442
—— ——, electrophoresis of, 93
—— ——, hyaluronic acid of, 211
—— ——, natural hydrocortisone in, 392
—— ——, serial tests of, in evaluation of therapy, 283
—— membrane, morphology of, *442
—— —— and mucoprotein viscosity, 412
Synovitis, pigmented villonodular, *303
Synovium, punch biopsy of, in knee, *443

TANG, J., 425
*TARANTA, A., 443
*TAYLOR, D., 303
*TAYLOR, G. D., 443
TEGNER, W. S.: *see* STOREY, G., and TEGNER, W. S.
Temperature of skin and sensitivity to pain, 397
Tendon, spontaneous rupture of, *303
Testosterone propionate (Testoviron) and peripheral vasculature, 293
Thighs, enlarged, and rheumatic pain, 386
THOMAS, A. E.: Chronic arthritis after recurrent rheumatic fever, 259
THOMAS, D. P. PAGE, and DINGLE, J. T. M.: Serum antiplasmin and plasmin in rheumatoid arthritis, 195
THOMPSON, M., *303, *442
——: *see* DUTHIE, J. J. R., THOMPSON, M., WEIR, M. M., and FLETCHER, W. BELL
Thorax involvement in spondylitis, 78
Thymol turbidity, 186
Thyroidectomy, experimental, 73
Thyrotrophin: hormone and thyroidectomized rats, 73
Tissue, connective, chemistry of, *105, 412
——, ——, diseases of, 413 *bis*
——, ——, metabolism, 238
——, ——, permeability of, 300
—— culture of synovial membrane, *442
——, mesenchymal, hormonal control of, 300
——, osseous, fluoride concentrations in, 382
——, ——, carcinoma and, 382
——, subcutaneous, and rheumatic pain (panniculitis), 385
TOMKINS, G., 100
Toxicity of hydralazine, *303
Trauma as cause of Heberden's nodes, 8
TRAUT, E. F., 440
TROMMER, P. R., 440
TURNER, J. C., 444
'Tyrosine', 195

Ultrasonic therapy, *303
Urate excretion in gout, salicylate and, 444
—— synthesis in gout, 433
Uricolysis in gout, 98, 409
Uricosuria, phenylbutazone and, 97
Urobilinogen, 185

VAILLANCOURT, DEG., *105, *303
Van Breemen, Dr. J., 80th birthday, 301

*VANCE, H. G., 105
Vasculature, peripheral, in arthritis, rheumatoid, 293
Vasculitis, nodular, 431
VAUGHAN, J. H., 431
Vertebrae, lumbar, pathology of, 302
VIGNOS, P. J., 431
*VIGODA, P., 443
VILLA, L., BALLABIO, C. B., and SALA, G.: Metacortandracin and 9-alpha-fluoro hydrocortisone acetate in rheumatic diseases, 251
Vitamin B_{12} in Felty's syndrome, 87

WAGNER, V., and REJHOLEC, V.: Agglutinins and incomplete antibodies after a single antigenic inoculation in normal and rheumatic individuals, 243
WAHLGREN, F.: *see* EGELIUS, N., GÖHLE, O., JONSSON, E., and WAHLGREN, F.
WAINE, H., 93
WALKER, S. J., 440
*WALLACE, S. L., 443
WALTHARD, K. M., 300
WARD, L. E., 101, 416, 421, *442
*WARNER, R. S., 442
*WARREN, J. E., 442
*WEDGEWOOD, R. I., 442
WEINBERGER, H. J., 430
WEIR, M. M.: *see* DUTHIE, J. J. R., THOMPSON, M., WEIR, M. M., and FLETCHER, W. BELL
WEST, H. F.: Effects of 9-alpha-fluoro hydrocortisone acetate on adrenal function, 170
——, 301, 302
——, 446
WIGZELL, F. W.: *see* ROY, L. M. H., WIGZELL, F. W., DEMERS, R., SINCLAIR, R. J. G., DUTHIE, J. J. R., ATHERDEN, S. M., and MARRIAN, G. F.
William Marsden Travelling Professorship, 210
*WILLIAMS, I., 212
WILSON, G. M., 97, 98, 434
*WOOD, P., 303
WOODMANSEY, A.: *see* BEATTIE, J. W., and WOODMANSEY, A.
——, and BEATTIE, J. W.: Effect of cortisone and certain other steroids on the peripheral vasculature in arthritis, 293
WRIGHT, V., 446
WROBLEWSKI, F., 425
WYNGAARDEN, J., 98, 433

YIELDING, K. L., 93
YOUNG, D., 425
YÜ, T. F., 434, 444
*YULES, J. H., 442

ZEVELY, H. A., 413, *442, *443
ZIFF, M., 94, 96, 97, 412, 444
Zinc hydroxide and corticotrophin in arthritis, rheumatoid, *104
—— turbidity, 186
ZUCKER, M., 98
——: *see* BIEN, E. J., and ZUCKER, M.

9-α-fluoro hydrocortisone acetate, 251
—— —— and adrenal function, 170
—— —— in arthritis, rheumatoid, 101 *bis*, 421
—— —— ——, chemical structure of, 422
17-hydroxy-20-oxosteroids, urinary excretion of, in arthritis, rheumatoid, 172
17-ketosteroids, urinary excretion of, and 9-α-fFa, 170

INDEX TO SUBJECTS OF ARTICLES ABSTRACTED

* indicates that only the title of the article is given

Acid, ascorbic, hormones and levels of, in man, 124
——, formic, in arthritis, 116
——, hyaluronic, of joint fluids, hydrocortisone and, 322
——, pantothenic, in lupus erythematosus, 117
——, silicic, in arthritis, 116
——, uric, isotopic, in gout and rheumatoid arthritis, probenecid and phenylbutazone and, 219
ACTH and adrenal cortex, 222, 323
—— and —— glands in nephrosis, 124
—— and —— weight, 459
—— in arteritis, temporal, 463
—— in arthritis, rheumatoid, *314
—— and ascorbic acid levels, 124
—— in Basedow's disease, 130
—— and β-17-ketosteroid excretion, *131
——, biological properties of, 323
—— in blood dyscrasias, 223
—— and cholesterol concentration, 459
—— and Cushing's syndrome, 462
——, eosinophil response to, salicylate and *para*-amino benzoate and, 458
—— and hepatic coma, *463
—— indications for, *463
—— inhibition by vitamin B_{12}, 463
——, intravenous, and 17-hydrocorticosteroid plasma levels, 456
—— in joint disease, *131 *bis*
—— in Landry-Guillain-Barré syndrome, 322
——, long-acting, containing zinc, 323
——, long-term therapy with, 123, 450
——, minimal doses of, in arthritis, rheumatoid, *314
—— in nephrosis, 459
—— in pellagra, 126
—— in pleurisy, tuberculous sero-fibrinous, 321
——, psychic disturbance due to, *131
—— in purpura, idiopathic thrombocytopenic, 125
—— ——, rheumatic, 314
—— in rheumatism, acute, 109, 448 *bis*
—— in temporal arteritis, 463
—— in tuberculosis pulmonary, 459, 460
—— and *x*-ray damage, 463
——/17-hydroxycorticosteroid response in children, 222
Acute rheumatism: *see* Rheumatism, acute
Adenotriphosphatase in shingles, *464
Addison's disease, aldosterone in, 127
—— ——, phenylbutazone in, 463
Adrenal cortex, ACTH and cortisone and, 323
—— —— and radiotherapy, 128
—— weight, hormone therapy and, 459
Adrenalectomy, glycyrrhizin in, 223
Adrenaline, *120
—— and adrenocortical secretion, 460
Adrenocortical function in pernicious anaemia, 125
—— secretion, adrenaline and, 460
Aged, osteo-arthritis in, *114
Albuminuria in arthritis, rheumatoid, 450
Aldosterone in Addison's disease, 127
——, anticortisol activity of, 462
—— in arthritis, rheumatoid, 458
——, colorimetric analysis of, *463
——, experimental, 324
—— and oedema, 458
—— in urine, 222
Allergy in endarteritis diffusa, 130
—— and gout, *121
α-haemolytic streptococcus in rheumatism, acute, *456
para-Aminobenzoate, 458
Aminotripeptase in synovial fluid, 319
d-Amphetamine, *120
Amyloid changes in arthritis, rheumatoid, 113, 450, *451
Anaemia, aplastic, after mepacrine in lupus erythematosus, *454
——, pernicious, adrenocortical steroids and metabolism of 17-hydroxycorticosteroids in, 125
Ankylosing spondylitis: *see* Spondylitis, ankylosing
Antagonism of ACTH and cortisone in an anticoagulant, 221
—— of corticoids, 221
Antibiotics with ACTH in pulmonary tuberculosis, 459
—— and lethal endotoxins in mice, 459
—— in rheumatism, acute, *110, *310
—— with steroid hormones in infections, 127 *bis*
Anticoagulants in rheumatism, acute, *110
Antigen-antibody reactions in arthritis, rheumatoid, 311
Antimalarial drugs in rheumatism, 117, 118
Antistreptolysin in rheumatism, acute, *321
Apresoline and arthritic syndrome, 113
Arteriosclerosis and Paget's disease, 224
Arteritis, temporal, ACTH in, *463
Arthritis, Bryson treatment of, 116
——, chronic, plastic injections in, 317
——, ——, radiotherapy of, 452
——, cobra venom in, 116
—— after desoxycorticosterone acetate and cortisone with adrenocortical hypofunction, *324
——, experimental, *119
——, ——, provoked by deoxycortone, 458
——, familial, 453
——, formic acid in, 116
——, gouty, 455
——, orthopaedic treatment of, 218
——, rheumatoid, ACTH in, *314, 450
——, ——, aetiology of, *314
——, ——, aldosterone in, 458
——, ——, amyloidosis in, 113, 450, *451
——, ——, aspirin compared with cortisone in, 112
——, ——, auto-antibodies in, 313
——, ——, autosensitization and, *217
——, ——, bile salt derivative in, 313
——, ——, blood pressure in, 111, *451
——, ——, Bufferin in, *451
——, ——, colloidal gold sulphide in, 112
——, ——, cortisol compared with cortisone in, 112
——, ——, cortisone in, 310, 311 *bis*
——, ——, —— compared with aspirin in, 112
——, ——, ——, ——, cortisol, 112
——, ——, crippling in, prevention of, 112
——, ——, diagnosis of, *451
——, ——, di-(2-chloroethyl)-hydrochloride in, 313
——, ——, in elderly, *114
——, ——, electromyography in, *451
——, ——, γ globulin in, 314
——, ——, gold-hormone therapy in, 451
——, ——, hydrocortisone injections in, 113, *113, 310, 322
——, ——, individual therapy of, *114
——, ——, joint fluid changes in, 450
——, ——, juvenile, *217
——, ——, lymphadenopathy of, *321
——, ——, management of, *217
——, ——, measurement of, by C-reactive protein, 220
——, ——, ——, ——, by serum polysaccharide/protein ratio, 219
——, ——, metacortandracin in, 312
——, ——, metacortandralone in, 312
——, ——, and muscle metabolism, *217
——, ——, nitrogen mustard in, 111
——, ——, orthopaedic management of, *314
——, ——, phenylbutazone in, 219, 453
——, ——, physical management of, *314
——, ——, placental serum in, *217
——, ——, pregnancy and, *451
——, ——, —— blood in, 112
——, ——, probenecid and, 219
——, ——, and psychosis, *217
——, ——, rehabilitation in, 114, *318 *bis*
——, ——, serology of, 121 *ter*, 122 *bis*, *123 *ter*
——, ——, serum changes in, *123
——, ——, skin testing in, 311
——, ——, surgery in, *114, *314
——, ——, turbidity test in, with mercuric chloride, *321
——, ——, Waaler-Rose test in, 313
——, ——, 9-α-fluoro hydrocortisone acetate in, 458
——, sacro-iliac, infective, *315
——, silicic acid in, 116

Arthritis, traumatic, *318, *455
Arthroplasty of hip, *114
——, acrylic, in spondylitis, ankylosing, 315
Arthrosis, acromio-clavicular, *120
——, climacteric, *114
—— and hormone, somatotrophic, *318
——, sub-astragaline, and arthritis, *224
Aschoff bodies and carditis, rheumatoid, 122
Aspirin compared with cortisone in arthritis, rheumatoid, 112
—— in rheumatism, acute, 109, *110, 448
Asthma, bronchial, cortisone in, 130, 321 *bis*
Atebrin: *see* Quinacrine
Auto-allergy and rheumatism, *224
Auto-antibodies in arthritis, rheumatoid, 313
Autosensitization and arthritis, rheumatoid, *217

Backache, traction in, 318
Ballistocardiograph in rheumatism, acute, *450
Basedow's disease, ACTH in, 130
Benemid, renal action of, *121
Bile salt derivative in arthritis, rheumatoid, 313
Blood dyscrasia, splenectomy, cortisone, and ACTH in, 223
——, human, corticotrophic activity of, 125
——, oximetry in, *310
—— oxygen in rheumatic carditis, 110
——, *p*H of, and serum protein fractions, *321
—— pressure, low, in arthritis, rheumatoid, 111
—— protein content in diagnosis of arthritis, rheumatoid, *123
—— proteins in rheumatism, acute, 448
—— vessels, permeability of, in rheumatism juvenile, 309
—— volume determinations in rheumatic heart disease, 305
Bottyán's antigen in diagnosis, 119
Brewing industry, rheumatism in, 218
Brucella abortus in detection of arthritis, rheumatoid, 313
Brucellosis, chronic rheumatism in, *218
Bryson treatment of arthritis, 116
Bufferin in arthritis, rheumatoid, *451
Burns, Robert, and his heart, 132
Butazolidin: *see* Phenylbutazone

Calcium balance and cortisone, 129
—— metabolism in sarcoidosis with hypercalcaemia, cortisone and, 223
Calcinosis and collagen diseases, 465
Capillary permeability and sodium salicylate, *321
Caplan's syndrome, *114, 216, 217 *bis*
Carditis, rheumatic, blood oxygen in, 110
——, ——, in children, 107
——, ——, cortisone in, 107
——, ——, death from, causes of, 449
——, ——, diagnosis of, *216, *310 *bis*
——, ——, focal pulmonary haemosiderosis in, 449
——, ——, hormones in, 110, *111, 306, 307, 308
——, ——, in Mexico, *310
——, ——, muscle damage and Aschoff bodies, 122
——, ——, in pregnancy, 110
——, ——, and rheumatism, acute, *110
——, ——, salicylate therapy in, 306, 308
——, ——, serum proteins in, *221
Cellulitis, subcutaneous: *see* Fibrositis, *218
Cheilotomy in osteo-arthritis, 314
Chemoprophylaxis in rheumatism, acute, 448
Children, blood phosphatase and serum vitamins in, *221
——, rheumatic carditis in, 107, 109
——, rheumatic, upper respiratory infections in, *216
——, rheumatism, acute in, 307, 308 *ter*, 309 *bis*, 448 *ter*
Chlorohydrocortisone, 461
Chlorpromazine, 457
Cholesterol concentration hormone therapy and, 459
Circulation in Sudeck's syndrome, *455
Cobra venom in arthritis, 116
Colitis, ulcerative, ACTH in, 125
——, ——, cortisone in, 126
Collagen disease, calcinosis in, 465
—— ——, corticoids in, 224
—— —— and inflammatory rheumatism, *454
—— ——, radiology of, *455
Colorimetric analysis of steroid hormones, *403
Commissurotomy, mitral, rheumatic crises provoked by, 305
Compound F: *see* Hydrocortisone
Convalescence after rheumatism, acute, in children, 308
Coombs test, 313
Copper in plasma in rheumatism, 312
Cordier-Chaix test of erythrocyte sedimentation rate in rheumatism, acute, 320
Corticoids, antagonism of, 221
—— in collagen disease, 224
Corticotrophin: *see* ACTH
Cortisol and adrenocortical capacity, 461
—— compared with cortisone, 112
Cortisone and adrenal cortex, 323, 462
Cortisone and weight, 459
——, antiphlogistic action of, 464
—— and ascorbic acid levels in man, 124
—— in asthma, bronchial, 130, 321 *bis*
—— in blood dyscrasias, 223
—— and calcium balance, 129
—— and —— metabolism, 223
—— in carditis, rheumatic, 107
——, chloro-derivative of, 129
—— and cholesterol concentration, 459
—— colorimetric analysis of, *463
—— compared with aspirin, 112
—— —— —— cortisol, 112
—— and endotoxin response, 324, 459
——, exophthalmos in rat after, 129
—— in Felty's syndrome, *113
—— and glucose tolerance test, 322
—— in gout, *219
—— in hepatic coma, *463
——, indications for, *463
—— in joint disease, *131
—— in Landry-Guillain-Barré syndrome, 322
——, long-acting ester of, 129
——, long-term therapy, 123, 310, 311 *bis*, 462
—— in peri-arthritis, 119
—— in pregnancy in arthritis, rheumatoid, *451
——, psychical disturbances due to, *131
—— in pulmonary tuberculosis, 126, 460
—— in purpura, idiopathic thrombocytopenic, 125
—— ——, rheumatic, 314
—— in rehabilitation, *131
—— in rheumatism, acute, 109, *110, *111, 215, 448 *bis*
—— in skin diseases, 130
—— in synovial fluid, 122
—— in temporal arteritis, *131
—— in tuberculous meningitis, 127
—— in ulcerative colitis, 126
—— and vitamin B_{12}, *463
—— —— D, 223
—— and *x*-ray damage, inhibition of, 459
C-Reactive protein determination as measure of rheumatoid activity, 220
Creatinuria, *221
Crippling, prevention of, in arthritis, rheumatoid, 112
Cushing's syndrome and ACTH, 462

Dactylo-trachelo-arthrotic syndrome, *114
Deformity, prevention of, 112
Deoxycortone and arthritis, experimental, 458
Dextran in nephrotic syndrome, 459
Diabetes mellitus, cortisone and glucose tolerance test in, 322
Diagnosis, blood protein content and, *123
——, Bottyán's antigen in, 119
Disk, cervical, herniated, traction in, *219
——, intervertebral, hydrophilic properties of nucleus pulposus, *455
——, ——, deterioration of, as cause of accidents, *455
——, ——, pain relief in sciatica due to herniation of, *455
——, lumbar, surgery of, *455
Di-(2-chloroethyl)-methylamine hydrochloride in arthritis, rheumatoid, 313

Elderly, arthritis, rheumatoid, in, *114
——, carditis, rheumatic, in, *110
——, cortisol and adrenocortical capacity in, 461
Electrocortin: *see* Aldosterone
Electromyography in arthritis, rheumatoid, *451
Electrophoresis in rheumatism, acute, 220, 221*, 447, 448, *456
Embolism prevention in carditis, rheumatic, 110
Emotional factors in rheumatic disease, *465
Endarteritis diffusa and allergy, 130
Endocrinology, surgical, 461
Endotoxin response and cortisone, 324
Enzymes in inflammatory reactions, *221
Eosinophil response and ACTH, 458
Eosinophils, 17-hydroxycorticosterone and, 320
Epicondylitis, radiotherapy of, 452
Erythrocyte sedimentation rate in rheumatism, acute, Cordier-Chaix test of, 320
—— —— —— and focal infection, *321
—— —— —— and anti-rheumatic agents, *119
Ethanol fractionation in haemagglutination tests, *451
Ethyl biscoumacetate, anticoagulant activity of, and steroid hormones, 221
Evaluation of therapy, *465
Exophthalmos in rat after cortisone or thyroidectomy, 129
Eyes in lupus erythematosus, 218, 454
—— in Paget's disease, 224
—— in spondylitis, ankylosing, 115
—— in Still's disease, 312

Felty's syndrome, cortisone in, *113
—— ——, splenectomy in, *113
—— ——, splenic neutropenia in, *123
Fever, rheumatic: *see* Rheumatism, acute
Fibroblasts in rheumatoid lesions, *321
Fibrositis, *218
Fluoridation of drinking water and bone formation, 224
Fluorohydrocortisone, 461
Flying and heart disease, 307
Focal infection and erythrocyte sedimentation rate, *321

Gamma globulin in arthritis, rheumatoid, 314
Glands, adrenal, and ACTH in nephrotic syndrome, 124
——, ——, —— in rheumatism, acute, 124
Glucose tolerance test and cortisone, 322
Glycuronic acid lactone and tissue hyaluronidase, *123
Glycyrrhizin after adrenalectomy, 223
Gold and hormone therapy in arthritis, rheumatoid, 451
—— in infective rheumatism, *464
——, oral, in arthritis, rheumatoid, 113
—— sulphide, colloidal, in arthritis, rheumatoid, 112
Gougerot-Sjögren syndrome, *119
Gout, *121 *ter*, 455
——, allergy and, *121
——, cortisone in, *219
——, H.P.C. in, 120
——, phenylbutazone in, 120, *121, 219
——, probenecid and phenylbutazone in, 219
——, spa treatment in, *121
G-15903: *see* Irgapyrin
G-25671, *120

Haemagglutination, 456
—— in arthritis, rheumatoid, 121, *221, *451
—— and complement changes in arthritis, rheumatoid, *123
Haemosiderosis, focal pulmonary, in rheumatic carditis, 449
Hand, arthritic, rehabilitation of, *318
Heart disease and rheumatism, acute, 305 *bis*, 306 *bis*, 307 *bis*
Heberden's nodes and dactylo-trachelo-arthrotic syndrome, *114
Heredity in rheumatism, acute, 447
Hip, arthroplasty of, *114
——, intra-articular hydrocortisone injection, *451
——, osteo-arthritis of, *114, *217, 314, *315
Histology, 320, *321
Hormone therapy in carditis, rheumatic, 306, 307, 308
—— —— in rheumatism acute, 110, *110, *111 *ter*
——, somatotrophic, and arthrosis, *318
H.P.C. in gout, 120
Hyaluronidase in inflammatory and degenerative disease, 220
—— in tissue and long-term treatment with glycuronic acid lactone, *123
Hydrocortisone, colorimetric analysis of, *463
—— in dermatoses, 126
—— and hyaluronic acid of joint fluids, 322
——, intra-articular, 118
——, ——, in hip-joint, *451
—— in joint disease, *455
——, mechanism of, 457
——, multiarticular injection of, 113, *113
——, oral, in arthritis, rheumatoid, 310, 311
—— in pollinosis, 130
—— in soft-tissue lesions, 464
—— and synovial fluid, 122, *456
—— in tennis elbow, 118 *ter*
—— and tissue culture, 128
Hypoglycaemia in Reiter's syndrome, 119

Industry, rheumatism in, 218, *224 *bis*
Infancy, rheumatism, acute, in, 449
Injury and arthritis, *318
Irgapyrin (G-15903), *120
Ischaemia, coronary, and peri-arthritis, 115
Isotopes, radioactive, in rheumatology, 132

Joint disease and disordered muscle metabolism, *318
—— ——, orthopaedic treatment of, *224
——, ——, prophylaxis of, *451
—— fluid in arthritis, rheumatoid, 450
—— ——, viscosity of, 320
——, Luschka, osteo-arthritis of, 314
——, sacro-iliac, *315 *ter*
—— temperature, procaine and, 316

Knee, osteo-arthritis of, *451
——, radiotherapy of, 452
"K317": *see* "Osadrin"

Lactone, glycuronic acid, and tissue hyaluronidase, *123
Landry-Guillain-Barré syndrome, ACTH in, 322
——, cortisone in, 322
Leukaemia, infantile, rheumatoid, *451
Liver function in rheumatism, *456
—— in lupus erythematosus, *454
Lumbago, vertebral, *455
Lung, rheumatoid disease of, *451
Lupus erythematosus, aplastic anaemia after mepacrine in ,*454
—— ——, hepatic dysfunction in, *454
—— ——, histology of, 320
—— ——, mepacrine in, 116
—— ——, nitrogen mustard in, 117
—— ——, ocular findings in, 218, 454
—— ——, pantothenic acid and Vitamin E in, 117
—— ——, prognosis of, *454
Luschka joints, osteo-arthritis of, 314
Lymphadenopathy of arthritis, rheumatoid, *321

Manipulation in low-back pain, 455
Meningitis, tuberculous, cortisone in, 127
Mepacrine in lupus erythematosus, 116
—— —— ——, aplastic anaemia after, *454
Mercuric chloride turbidity test in arthritis, rheumatoid, *321
Metabolism, muscular, disordered in rheumatoid joint disease, *318
—— of phenylbutazone in man, *465
Metacortandracin in arthritis, rheumatoid, 312
Metacortandralone in arthritis, rheumatoid, 312
Methylandrostenediol and calcium balance, 129
Mitral stenosis and rheumatism, acute, 305
—— valve, rheumatic restenosis of, *450
Mucoproteins in rheumatism, acute, in infancy, 449
Muscle damage and Aschoff cells in carditis, rheumatic, 122
—— metabolism in arthritis, rheumatoid, *217

^{24}Na and synovial exchange, 116
Nephrosis, sodium restriction in, 459
——, Dextran in, 459
——, ACTH in, 459
——, nitrogen mustard in, 459
Nephrotic syndrome, ACTH and adrenals in, 124
Neurology and rheumatism, *224
Neuropathy, peripheral, in periarteritis nodosa, 217
Neutropenia, splenic, in Felty's syndrome, *123
Nitrogen mustard in arthritis, rheumatoid, 111, 313
—— —— in lupus erythematosus, 117
—— —— in nephrotic syndrome, 459
Nodules, dural, in arthritis, rheumatoid, *123
——, rheumatoid, unusual, *314

Orthopaedics in arthritis, rheumatoid, *218, 221, *314 *bis*
—— in osteo-arthritis, *114
"Osadrin", *318
Osteitis deformans: *see* Paget's disease
Osteo-arthritis in aged, *114
——, cervical, neurologic complications of, *114
——, ——, with radiculitis, 318
——, cheilotomy in, 314
—— deformans of Luschka joints, 314
—— of hip, *114, *217, 314, *315
—— of knee, *451
——, multiple perforations in, 314
——, orthopaedic treatment of, *114
——, pathogenesis of, *114
——, rest in, 114
——, sterno-costo-clavicular, *114
Osteo-arthropathy, pulmonary, diagnosis of, 318
Osteo-arthrosis, tissue therapy in, *114
Osteo-phytosis, experimental, *114
Osteoporosis circumscripta: *see* Paget's disease
Oxygen in blood in carditis, rheumatic, 110

Paget's disease, ocular changes in, 224
—— ——, radiography of petrous bone in, 454
—— —— of skull, 453
Pain, cervico-brachial, *120
—— in chronic rheumatism, *224
——, low back, management of, 218
——, ——, manipulation in, 455
——, neck, 219
——, relief of, in sciatica due to herniation of intervertebral disk, *455
Pancytopenia: *see* Felty's syndrome
Pellagra, ACTH in, 126
Penicillin in prevention of rheumatism, acute, 109
Periarteritis nodosa, diagnosis, 317
—— ——, peripheral neuropathy in, 217
Peri-arthritis, oral cortisone in, 119
——, radiotherapy of, 452
——, scapulo-humeral, and coronary disease, 115
Peripheral circulation and rheumatic disease, 464 *bis*, *464 *bis*
Phenylbutazone, antiphlogistic action of, *464
—— in arthritis, rheumatoid, *120 *bis*, 453, *465
——, DCA-like effect of, 463
—— in gout, 120, *121, 219

Phenylbutazone, metabolism of, in man, *465
—— in rheumatism, acute, *216, 305, *465
Physiotherapy in rheumatism, degenerative, 316
Plasma copper in rheumatism, 312
——, steroid level in, and salicylates, 124
Plastic material, injection of, in arthritis, chronic, 317
Pleura, rheumatoid disease of, *451
Pleurisy, tuberculous sero-fibrinous, ACTH in, 321
Pneumoconiosis and arthritis, rheumatoid: *see* Caplan's syndrome
Pneumonia, rheumatic, 214
Pollinosis, hydrocortisone in, 130
Polyarthritis and silicosis, 216, 217
Porphyrin, erythrocyte, in rheumatism, 312
Potts' disease, lumbar, *132
Pregnancy, blood transfusions in arthritis, rheumatoid, 112
—— in arthritis, rheumatoid, *451
——, rheumatic carditis in, 110
Pressure, arterial, and arthritis, rheumatoid, *451
Probenecid in gout, 219
Procaine, periarticular, and joint temperature, 316
Prophylaxis of rheumatism, acute, in children, 308, *310 *bis*, *465
Psoriasis, *120 *bis*
—— spondylitica, 451
Pseudo-rheumatism, *224
Psychic disturbance after hormone therapy, *131
Psychosis and arthritis, rheumatoid, *217
Purpura, idiopathic thrombocytopenic, steroid hormones and, 125
——, rheumatoid, ACTH in, 314
——, ——, cortisone in, 314
——, ——, "4560 RP" in, 314
Pyrazolidin, *120

Quinacrine in lupus erythematosus, *119
Quinoline antimalarial derivative in rheumatism, 117
Q-Tc in diagnosis of carditis, rheumatic, *310

Radiculalgia, idiopathic crural, *120
Radiculitis with osteo-arthritis, cervical, 318
Radiography, *120
—— in Paget's disease, 454
Radiology of collagen disease, *455
—— of peripheral circulation, 464
Radiotherapy and adrenal cortex, 128
—— of arthritis, 452 *bis*
—— epicondylitis, 452
—— periarthritis, 452
—— spondylitis, 315, 452
Raynaud's phenomenon due to vibrating tools, 131, 132
Rehabilitation, *132
—— in arthritis, rheumatoid, *114, *318 *bis*
——, cortisone in, *131
—— in rheumatism, *224
Reiter's syndrome, 119 *bis*, *119, 454
Rheumatic fever: *see* Rheumatism, acute
Rheumatism, acute, abortive, 216
——, ——, ACTH in, 448 *bis*
——, ——, —— and adrenals in, 124
——, ——, aetiology of, *110 *bis*, *450
——, ——, antibiotics in, *110, *216
——, ——, anticoagulants in, *110
——, ——, aspirin in, 448
——, ——, ballistocardiograph in, *450
——, ——, biological findings in, 447
——, ——, blood oximetry in, *310
——, ——, —— blood volume determinations in, 305
——, ——, and carditis, rheumatic, *110
——, ——, chemoprophylaxis of, 448
——, ——, in children, 107, 109, 307, 308 *ter*, 309 *bis*, 448 *ter*, *450
——, ——, community control of, *310
——, ——, cortisone in, *110, *111, 215, 448 *bis*
——, ——, death from, causes of, 449
——, ——, diagnosis of, *216 *bis*, 304, *310 *bis*
——, ——, in elderly, *110
——, ——, electrophoresis in, 220, *221
——, ——, erythrocyte sedimentation rate in, 320
——, ——, experimental, 108
——, ——, flying and, 307
——, ——, follow-up studies of, *450
——, ——, heart surgery and, 305 *bis*
——, ——, heredity in, 447
——, ——, hormone therapy in, 110
——, ——, hypersensitivity in, *110
——, ——, in infancy, *110, 449
——, ——, management of, *110
——, ——, in Mexico, *310
——, ——, in military personnel, 305
——, ——, mitral commissurotomy and, 305
——, ——, murmurs in early heart disease, 306
——, ——, penicillin in, 109
——, ——, phenylbutazone in, *216, 305
——, ——, prevention of, 107, *110 *bis*, *216, 308, *310 *bis*
Rheumatism, acute, salicylates in, 215 *bis*, *216, *110
——, ——, —— and Vitamin C stores in, *450
——, ——, scarlet fever and, 215
——, ——, sequelae of, in men, 215
——, ——, serology of, 108 *bis*, 109 *bis*, *321
——, ——, streptococcal infection and, *310, 448
——, ——, streptococci, group-A β-haemolytic in, 307
——, ——, streptolysin-S in, 108
——, ——, therapy of, *216, 304, 306
——, ——, visceral lesions in, *310
——, ——, vitamin A in, 214
——, degenerative, physiotherapy in, 316
——, emotional factors in, *465
——, experimental, 310
——, ——, induced by polysaccnarides from *Klebsiella pneumoniae* Type B, 309
——, infective, gold salts in, *464
——, juvenile, and vessel permeability, 214, 309
——, ——, fresh air treatment of, 309
——, non-articular, *456
——, ——, hydrocortisone in, 124
——, palindromic, *464
——, phenylbutazone in, *465
——, prophylaxis of, *465
——, psychogenic, *120
—— resembling arthritis, rheumatoid, *451
Rheumatoid arthritis: *see* Arthritis, rheumatoid

Sacro-iliitis, *115
Salicylate, antiphlogistic action of, *464
—— in carditis, rheumatic, 306, 308
—— and eosinophil response to ACTH, 458
—— and plasma 17-hydrocorticosteroids, 124, 460
—— in rheumatism, acute, 215 *bis*, *216
—— and urinary excretion of steroids, 123
—— and vitamin C reserves in rheumatism, acute, *450
Scarlet fever and rheumatism, acute, 215
Sciatica, relief of pain in, *455
Scleroderma, 317
——, disseminated, alimentary tract in, 115
Serology of rheumatism, 121 *bis*, 122 *bis*, *321 *ter*
—— of rheumatism, acute, 108 *bis*, 109 *bis*, *456 *ter*
Serum, placental, in arthritis, rheumatoid, *217
—— polysaccharide/protein ratio as measure of rheumatoid activity, 219
—— proteins, 121
—— —— in carditis, rheumatic, *221
—— —— fractions and blood *p*H in rheumatism, *321
—— ——/polysaccharide ratio and phenylbutazone, 453
Shingles, adenotriphosphatase in, *464
Shoulder, painful, 463
Shoulder-hand syndrome, *454
Silicosis and polyarthritis, 216, 217
Sjögren's syndrome, 119, *119, *221
Skin disease, cortisone in, 130
—— —— in rheumatism, *224 *ter*, 311
—— tests in arthritis, rheumatoid, 311
Skull, osteoporosis of, 453
Sodium radioactive (^{24}Na), 116
—— restriction in nephrosis, 459
—— salicylate, biological activity of, *310
—— —— and capillary permeability, *321
—— —— and 17-ketosteroid excretion, *456
—— triketocholanic acid (bile salt derivative) in arthritis, rheumatoid, 313
Spa treatment for gout, sthenic, *121
Spinal pumping in arthritis, *464
Spine, cervical, and osteo-arthritis, neurology of, *114
Splenectomy in blood dyscrasia, 223
—— in Felty's syndrome, *113
Spondylitis, ankylosing, acrylic arthroplasty in, 315
——, ——, aetiology of, *452
——, ——, and breathing, 452
——, ——, of delayed onset, *217
——, ——, ocular symptoms in, 115
——, ——, radiotherapy, 315, *452
——, infective, *115
Spondylosis, cervical, 218
Stenosis, mitral, and rheumatism, acute, 305
Sterno-costo-clavicular joint, osteo-arthritis of, *114
Steroids, adrenocortical, urinary excretion of, and salicylates, 123
——, ——, plasma level of, and salicylates, 124
—— hormones with antibiotics in severe infections, 127
——, —— in experimental infections, 128
Still's disease as adaptation syndrome, *114
—— ——, ocular signs in, 312
Streptococci, group-A β-haemolytic, and rheumatism, acute, 307, *310
Streptolysin-O, skin test with, 109
Streptolysin-S in rheumatism, acute, 108
Stress, systemic and local, 123

Sudeck's syndrome, circulation in, *455
Surgery in arthritis, rheumatoid, *114, *314
—— in heart disease and rheumatism, acute, 305 *bis*
—— in lumbar disk protrusion, *455
—— in tenosynovitis, *454
Synovial fluid, aminotripeptase content of, 319
—— ——, concentration of intra-articularly injected hormones in, 122
—— ——, hydrocortisone and, *456
—— ——, properties of, *123
Synovium, investigation by radioactive sodium (^{24}Na), 116

Temporal arteritis, cortisone in, *131
Tennis elbow, hydrocortisone in, 118 *ter*
Tenosynovitis, rheumatic, surgery in, *454
Testis hyaluronidase, activity of, and serum, *456
Therapy, evaluation of, *465
Thorn's test, 319
Thyroid function and rheumatic tissue reactions, *465
Thyroidectomy, exophthalmos in rat after, 129
Thyroiditis, rheumatic, *120
Tissue, rheumatic, reactions of, and thyroid function, *465
Traction in backache, 318
Trauma, surgical, and effects on metabolism, 461
Tuberculin arthritis, experimental, *119
Tuberculosis, pulmonary, hormone therapy of, 126, 459, 460
Turbidity test with mercuric chloride, *321

Urethritis, non-gonococcal, and arthritis, *119
Urine, excretion of adrenocortical steroids in, and salicylate therapy, 123

Valve, mitral, rheumatic restenosis of, *450
——, ——, stenosis of, 305
——, ——, surgery of, 305
Viscosity anomalous in joint fluid, 320
Vitamin A in rheumatism, acute, 214
Vitamin B_{12} inhibiting steroid hormone therapy, *463
Vitamin C and salicylates in rheumatism, acute, *450
Vitamin D and calcium balance, 129
—— and cortisone, 223
Vitamin E in lupus erythematosus, 117

Waaler-Rose reaction, *123, *221, 313
Work, rheumatism and, *464

Zinc in ACTH, long-acting, 323

9-α-fluorohydrocortisone acetate in arthritis, rheumatoid, 458
—— —— ——, experimental, 324
17-hydroxycorticosteroids and ACTH in children, 222
—— in body fluids, *324
—— in Cushing's syndrome, 462
—— in plasma, ACTH and, 456
—— ——, salicylates and, 460
—— metabolism in pernicious anaemia, 125
—— and surgical trauma, 461
17-hydrocorticosterone and eosinophils, 320
17-ketosteroid excretion and sodium salicylate, *456
"4560 RP" in purpura, rheumatoid, 314

INDEX TO AUTHORS OF ARTICLES ABSTRACTED

* indicates that only the title of a paper or article is given

Abd El Wahab, E. M., 456
*Ablard, G., 216, 305 *bis*
Abrams, H. L., 115
*Adams, F. H., 216
*Aikawa, J. K., 110
*Albanese, A. A., 450
Albert, A., 125
*Alexander, W. D., 123
*Allaria, A., 120
Allen, G. E., 311
Alram, D., 447
American Heart Association, 448
*Amouyal, J., 451
Anderson, J., 223
*Arbeit, S. R., 450
Arlet, J., *119, *316
Armato, A., 314
Arnulf, G., 317
*Aronsson, H., 120
*Arsov, D., 120
Attal, C., 110
d'Aubigné, R. M., 315
*Avery, W. G., 450
Axelrad, B. J., 458

Baader, E. W., 217
*Baccarini, V., 321
Bach, J., 308
*Bacri, J., 451
Baker, C., 324
Baker, E., 459
Balch, H. E., 127
Ball, M. R., 461
*Banghart, H. E., 120
Barata, M. I., 124
Barbieri, M., 314
*Barceló, P., 115
Barford, P., 463
*Barroso-Moguel, R., 321
*Basset, G., 456
Batalla, E., 313
Bayles, T. B., 314
Bayliss, R. I. S., 124, 322, 460
Bean, W. B., 111
Beck, J. C., 124
Beckett, A. G., 125
*Beelar, V. P., 113
Ben, M., 324
Benichoux, P., 317
*Bennett, H. N., 310
Berkowitz, D., 305
*Berthier, L., 217
*Bertrand, A., 310
*Besson, F., 310
Besson, L., 121
Bettley, F. R., 116
Beyer, A., 219
Bilka, P. J., 451
*Binks, F. A., 118
*Biorck, G., 450
Bishop, C., 219
Bishop, J. M., 110
Bisyarina, V. P., 214, 309
*Blankenheim, H., 224
Blankenhorn, M. A., 317
Blockey, N. J., 119
Blumenfeld, S., 318
*Blumensaat, C., 455
Boas, N. F., 129
*Böni, A., 464
*Boesman, T., 114
Boling, L., 127
Bollet, A. J., 312
*Bonard, E. C., 119
Bongiovanni, A. M., 462
Bonmann, K. H., 452
Bonner, C. D., 323
*Bonnet, H., 310
*Bonola, A., 114
*Bopp, A., 456
*Bordier, P., 311
Bourel, M., 116
Bourne, G., 307
Bouvrain, Y., 305
Brachman, P., 314
Brain, R., 218
*Bramwell, C., 310
Bray, P. F., 222
Bricaire, H., 319, 458
Brockbank, W., 321 *bis*
*Brodie, B. B., 465
*Brodkin, H. A., 131
*Brous, M., 464
Browne, J. S. L., 124
*Browning, J. S., 465
Brunelli, M. A., 109
Bryson, K. D., 116
Buchan, J. F., 454
Bullock, J. A., 219
Bundick, W. R., 320
Bunim, J. J., 311, 312
*Bunn, W. H., 310
Burley, D., 114
*Burns, J. J., 465
Burrage, W. S., 130

Callow, R. K., 129
Campo, C., 447
Caramanian, M., 110, *110, 305, 307
*Cardell, B. S., 221
Carnes, W. H., 115
*Caroit, M., 321
Carryer, H. M., 130
Carter, Y., 309, 310
Cartesegna, F., 313
Cartwright, G. E., 125
Cary, S. K., 125
*Casolo, G., 221
*Castagnoli, M., 120
*Castaigne, A., 119
*Castelli, D., 123
Catanzaro, F. J., 448
Cates, J. E., 458
Cave, A. J. E., 314
*Cecchi, E., 318
*Cerda C, M., 120
Certonciny, A., 118
Chamovitz, R., 448
Chaptal, J., 447
*Chapuis, R., 114
Charleux, G., 130
Chatterjee, J. B., 221
*Chevallier, J., 456
*Chevéz, A., 321
*Chiti, E., 217
Clark, E. J., 109
*Clark, I., 463
Clarke, E., 322
Clautour, J., 316
Clifton, F., 454
Cochran, J. B., 126
*Coke, H., 456
*Colinet, E., 456
Collins, D. H., 453
*Conn, H. L., 110
Conn, J. W., 322
*Conner, S. K., 465
*Conterno, G., 110
Cooper, R., 322
*Cop, D., 455
Cope, C. L., 222
Corbelli, G., 109
Costa, F., *120, *455
Costa Bertani, G., *131, *224, *464
Coste, F., 116, *456, *463
*Costero, I., 321
*Courjaret, J., 121
Courrault, R., 308
Cowan, T. W., 218
Coyer, A. B., 455
Creveld, S. van, 448
Crisp, E. J., 464
Crittenden, J. O., 122
*Currie, J. P., 120
*Curwen, I. H. M., 455
Curzio, A., 221

Dagonet, Y., 308
Daneo, V., *123 *ter*, *221, 313
*Daniels, R. S., 310
*Danopoulos, E., 120
Danowski, T. S., 459
Daum, K., 111
*Davalli, C., 455
Davis, L. L., 307
*Davison, S., 217
Dawidowicz, A., 119
*de Azua-Dochao, L., 224
*Debeyre, J., 132
Debeyre, N., 311
*Delaude, A., 119
*Delaville, G., 114
*Delbarre, F., 463
Deltour, G., 319
*Denis, A., 131
Dent, C. E., 223
Derriks, R., 459
Desaulles, P., 129
*Desestres, —, 111
Desproges-Gotteron, R., 316
*Destefanis, E., 110
Destombes, A., 314
*Dias Velloso, G., 120
Dick, A. P., 125
*Dickgiesser, F., 221
*Dilallo, R., 450
di Matteo, J., 308
Dohan, F. C., 122
*Dolan, M. A., 450
Dombre, —, 130
Donald, K. W., 110
Done, A. K., 460
*Dresner, E., 314
*Drew, J. F., 224
*Drieux, H., 114
*Druckmann, A., 452
*Drudi, C., 456
Dubois, E. L., 117, *119
*Dubois, R., 450
Duff, I. F., *314, 450
*Dupré, A. L., 217
*Durman, D. C., 318
Duryee, A. W., 317

Eaton, J., 115
Eberlein, W. R., 462
*Edström, G., 110
Egelius, N., 322
Eik-Nes, K., 125, *324, 456, 461
*Einaudi, G., 123 *bis*
Eisler, M., 324
Elingshausen, H. P., 452
Elliott, R. H. E., 223
Ellis, F. A., 320
Ely, R. S., 222, 460
Engleman, E. P., 120, 215, 462
*Ensign, D. C., 318
*Enzinger, J., 131
*Epstein, N., 216
Eskin, I. A., 323
Espacio, L., 313
Esposito, M. J., 449
Eyquem, A., 121

Fabre, J., 127
*Fähndrich, W. H., 451
*Fairburn, D., 455
Fajans, S. S., 322
Fantuzzi, B., 449
Farr, C. H., 453
Favour, C. B., 314
Fearnley, G. R., 450
Feriozi, D., 124
Ferrand, M., 304
*Ferraris, F., 310
*Fessler, J. H., 123
*Feyrter, F., 464
Firor, W. M., 116
Fischer, F., 129
Fischgold, H., 454
Fisher, B. M., 127
*Fitting, W., 224
*Fleming, J. L., 318
Fletcher, E., 316, 451
Florentin, A. A., 461
*Forest, A., 119
Forestier, J., 112, 115, 118
*Fornara, P., 451
Forsham, P. H., 120
Fortin, P., 305
Fowlks, E. W., 318
Foz, A., 122, 133
*Fränkel, M., 452
*Frain, J. B., 120
Fraisse, J., 447
François, J., 312
Françon, F., *110, *121
*Françon, J., 121
*Franz, A., 120
Frazer, E. H., 318
Fredell, E. W., 462
Freeland, D. E., 118
*Freislederer, W., 221
*Fremont-Smith, P., 451
Fruchart, G., 314

Gabriel, J. B., 463
*Galli, G., 455
*Galloway, L. S., 221
Gamna, G., 306
Gamp, A., *119, *123, *456
Garcia-Llaurado, J., 222
*Gaudin, G., 217
Geller, P., 459
Gelli, G., 306
Gennes, L. de, 319, 458
Germain, D., 320
Geyer, S., 305
*Ghanem, M. H., 464
Gilbert-Dreyfus, —, 128
Gilgenkrantz, J. M., *216, 305
Gillespie, W. A., 109
*Gioanni, T., 111
Girard, C., 305
*Giraud, G., 310, 453
*Girerd, G., 216
Goldfien, A., 120, 461
*Goldstein, A. S., 318
Goldthwait, J. C., 314

*Goldwater, L. J., 224
Goldzieher, J. W., 459
*Gomez Orbaneja, J., 224
*Goodwin, S., 465
*Gospodinoff, A., 321
*Gould, I. D., 451
Goulding, R., 221
Gray, C. H., 123
Green, T. W., 120
Greene, M. H., 307
Greenman, L., 459
Greer, C. H., 454
*Gregoris, L., 456
Gribble, M. de G., 118
Griffiths, J. D., 314
*Gros, H., 456
Grosfield, H., 128
*Gross, D., 224
*Grubb, K. P., 111
Grumbach, M. M., 462
Guez, A., 460
Guillon, J., 319
*Gulotta, G. A., 310
*Gurling, K. J., 221
Gutner, L. B., 318
Gvelesiani, K. G., 309

Hässler, E., 215
*Halhuber, M. J., 465
*Hall, P., 450
*Harkness, A. H., 119
Harper, C., 223
*Harris, S. B., 464
*Harris, T. N., 110
Hart, F. Dudley, 114
Hart, M., 219
*Harter, F., 221
Hastrup, B., 129
*Haus, E., 465
Haustrate, L., 312
Haydar, N. A., 461
Heathfield, K. W. G., 217
*Hebbert, F. J., 110
Heffer, E. T., 107, 220 *bis*
Hellbaum, A. A., 219, 453
*Heller, G., 451
Hench, P. S., 458
Henderson, L. L., 130
Henneman, P. H., 130
Henriksen, E., 130
*Herbert, J. J., 114
Hess, P., 452
*Higgons, R. A., 450
Highton, T. C., 313
*Hiller, E., 465
Hilton, G., 315
*Hines, J. J., 111
Hodges, R. E., 111
Hollander, J. L., 122
Hollister, L. E., 215
*Hollmann, S., 123
Holt, K. S., 215 *bis*
Holzbauer, M., 457
Homburger, F., 323
*Horning, E. C., 465
*Horton, W. G., 455
Houghton, L. E., 459
*Houli, J., 120
Houser, H. B., 109
*Howard, L. D., 454
Hudson, B., 320
Hudson, P. B., 223
Hunter, J. D., 460
*Hunziker, H., 121
Huriet, C., *216, 305
*Hursh, L. M., 324
*Hussel, W., 318
*Hutchison, H. E., 123
Hyman, G. A., 223

Illingworth, R. S., 215
*Inama, K., 465
Irby, R., 310
Irwin, J. W., 130
*Isemein, L., 455
Ishmael, W. K., 219, 453

Jackson, R. L., 448
*Jackson, W. M., 318
Jacobs, A. L., 214
Jacobs, J. H., 316
*Jacobson, A. S., 451
Jacqueline, F., 121 *bis*
Jahn, J. P., 127
*Jarvinen, K. A. J., 451
Jawetz, E., 128, 459
Jean, R., 447
Jeffrey, M. R., 312
Jepson, R. P., 132
*Jewett, H. B., 318
Jochem, E., 121
Johnson, B. B., 458
*Johnson, G. C., 454
Johnson, H. P., 120, 462
Jones, D. E. A., 459
Jones, R. S., 309, 310
Jonsson, E., 322
Josephs, C., 112
Josserand, A., 320
*Jurmand, S.-H., 120
Juster, M., 454
Justin-Besançon, L., *114, *321

Katz, H. M., 463
Kelley, V. C., 222, 460
Kellgren, J. H., 119
Kelly, H. G., 448
Kelly, M., 112
Kendall, P. H., 464
*Kibler, M., 114
*King, R., 114
Kinsell, L. W., 127
*Kirnberger, E. J., 456
Klein, R., *132, *464
Klotz, H. P., 460
*Knobová, J., 131
Knowles, H. C., 317
*Kobes, H. R., 217
Koelsche, G. A., 130
*Kofman, S., 454
Kolb, F. O., 215
*Kolodny, M. H., 451
Krautzun, K., 452
*Krewer, B., 113
Kroop, I. G., 107, *111, 220 *bis*
Krupp, M. A., 120, 462
*Kruskemper, H. L., 465
Kuhns, J. G., *114 *bis*, *218, *224
Kuipers, R. K. W., 118
*Kukowka, A., 321
*Kulonen, E., 456

Labesse, J., 308
*Lacapère, J., 114, 117
Lackner, R., 450
Lacrosaz, —, 130
Lafargue, J., 128
Laidlaw, J. C., 461
*Laine, V., 451
Landing, B. H., 124
Langeron, L., 314
Lansbury, J., 111, 311
Larcan, A., *216, 305 *bis*
*Laroche, C., 121
*Latour, H., 310
Layani, F., 310
Leathem, J. H., 324
Leb, A., 464
Lebeurre, R., 132
*Lebon, J., 451
LeBrie, S. J., 324
Lederer, J., 459
*Lee, P. R., 114
*Leikola, E., 454
Leinwand, I., 317
Leitner, Z. A., 214
Lemaire, E., 314
*Lenoch, F., 131
Leovy, W. A., 127
*Lepow, I. H., 451
Leu, H. J., 216, *464
*Levy, A., 310
Lévy, R., 113
Lièvre, J. A., 454
Likoff, W., 305
Lindahl, A., 113
*Lindholm, R. V., 114
Lloyd, J., 129
Lloyd-Roberts, G. C., 314
*Long, C., 318
Long, D. A., 129
*Lopez, B., 224
Lorber, J., 215
Lorch, P., 113, *113
*Lovgren, O., 463
*Lowman, E. W., 114
Lucherini, T., *120 *bis*, *318
Luetscher, J. A., 458
Luger, N. M., 463
*Luisada, A. A., 216
Lumpkin, W. R., 116
Lunnon, J. B., 123
Lutterbeck, H., 220

*McCarty, M., 216
McCauley, H. B., 224
McClure, F. J., 224
McDonald, I., 452
McEwen, C., *216, 311
McGehee, E. H., 123
McGrath, A. K., 462
Mach, R. S., 127
Mackenzie, K. R., 124
*McKusick, V., 450
MacLean, K., 119, 123, 221
MacLeod, M., 110
*Maffei, G., 321
*Maggi, C. A., 221
*Maher, J. A., 123
Mainland, D., 319
Mak, G., 448
*Makinen, P., 456
*Mangelson, F. L., 221
Mannes, P., 459
Marchand, J. H., 316
*Marks, G. H., 451
Marquezy, R. A., 308
*Mars, G., 114
Marshall, J., 131
*Martorelli, J., 218
Mason, H. L., 458
Massell, B. F., 458
*Massin, M., 119
*Mastragostino, S., 114
*Masturzo, A., 464
Mathieu de Fossey, B., 319
Mattox, V. R., 458
Maxwell, R., 324
May, F., 218
*Mayerhofer, E., 114
Meagher, T. R., 127
Medical Research Council, 112, 448
Meier, R., 129
*Melissinos, K., 120
Menkin, V., 457
Merrill, E. R., 459
Michaud, P., 115
Michel, J., 454
*Michotte, L., 454
*Mikkelsen, W. M., 314
*Miller, S., 114
Miniconi, P., 304
*Mintz, B., 224
Miowski, D. K., 126
Mittelman, A., 223
Monier, H., 117
Moore, F. D., 461
Moore, T., 214
*Moreau, C., 132
Morel, F., 116
*Moreno, B. A., 224
Morin, G., 317
Morris, A. J., 448
*Morris, J. E., 120
Mozziconacci, P., 110, 307
*Murley, A. H. G., 118
Myrden, J. A., 461

Nabarro, J. D. N., 222
*Natale, P., 120
*Naylor, A., 455
Needham, C. D., 452
Nelson, D. H., 125, *324, 456
Neuhaus, C., 449
*Neustadt, D., 120
*Neuwirth, E., 114
*Newman, M. K., 318
Newns, G. R., 112, 450
Nicaise, R., 459
Nogueira Cardoso, M. A., 214
*Norman, A., 463
Nouaille, J., 110
Nuffield Foundation Joint Committee on Cortisone, ACTH, and Other Therapeutic Measures in Chronic Rheumatic Diseases, 112
Nussenzveig, I., 214
Nussenzveig, V., 214

O'Connell, P. A., 458
*d'Oelsnitz, M., 111
*Offret, G., 119
*Ogston, A. G., 123
*Oswald, H., 123

*Padovani, J., 455
Page, F., 116
Palić-Szántó, O., 119
Palmer, J. G., 125
*Paolaggi, J., 121
Papagni, L., *120, *455
Paris, J., 125
Pasquariello, G., *310, *321
Pasquet, P., 304
Pasquet, V., 304
*Paton, M. D., 454
Patrick, D. R., 219
Paul, W. D., 111
Payne, R. W., 219, 453
*Peabody, C. W., 314
Pechet, M. M., 312
Perry, C. B., 109
Perry, W. D., 448
*Peterman, E. A., 221
Peters, G. A., 130
*Petersén, I., 451
Peterson, H. H., 127
*Peterson, W. L., 310
Petry, H., 216
*Petty, H., 314
Peyron, J., 310
Philpot, G. R., 223
Pietruschka, G., 224
*Pilorgé, D., 216
Pimenta de Campos, E., 214
*Pinheiro Martins, A., 120
Piñol, J., 311
Podberezec, M., 223
*Pohl, W., 224
*Poli, M., 110
Polley, H. F., 458
Poole, E. W., 131
Postel, M., 315
Poujade, L., 308
Power, M. H., 458
Prickman, L. E., 130
Pridie, K. H., *217, *315
Prosperi, P., 127
*Puech, P., 310

*Quin, C. E., 118

Ragan, C., 128
Raile, R. B., 222
*Raleigh, G. W., 217
Ramadier, J. O., 315
Rammelkamp, C. H., 448
*Rankin, J., 110
Rankin, J. de W., 309
Ratschow, M., 464
*Ravault, P., 217
Rawls, W. B., 459
Raynaud, R., 304
Reale, A., 305
*Reichenthal, J., 465
Reiman, J., 463
Rendle-Short, J., 215
Renold, A. E., 461
Reynard, W. A., 131
*Rezzonico, G., 224
*Rhodes, P. H., 310
Rich, H., 308
Richards, D. G., 224
Richards, M. T., 114
Richardson, E. M., 122
Richter, M. N., 317
*Riddell, M. J., 454
*Ritama, V. V., 451
Rivano, R., *217, *221, *318
*Rivera, M. E., 451
Robecchi, A., *221, 313, *454
Robert D'Eshougues, J., 304
*Roberts, E., 110

INDEX TO AUTHORS OF ARTICLES ABSTRACTED

* indicates that only the title of a paper or article is given

Abd El Wahab, E. M., 456
*Ablard, G., 216, 305 *bis*
Abrams, H. L., 115
*Adams, F. H., 216
*Aikawa, J. K., 110
*Albanese, A. A., 450
Albert, A., 125
*Alexander, W. D., 123
*Allaria, A., 120
Allen, G. E., 311
Alram, D., 447
American Heart Association, 448
*Amouyal, J., 451
Anderson, J., 223
*Arbeit, S. R., 450
Arlet, J., *119, *316
Armato, A., 314
Arnulf, G., 317
*Aronsson, H., 120
*Arsov, D., 120
Attal, C., 110
d'Aubigné, R. M., 315
*Avery, W. G., 450
Axelrad, B. J., 458

Baader, E. W., 217
*Baccarini, V., 321
Bach, J., 308
*Bacri, J., 451
Baker, C., 324
Baker, E., 459
Balch, H. E., 127
Ball, M. R., 461
*Banghart, H. E., 120
Barata, M. I., 124
Barbieri, M., 314
*Barceló, P., 115
Barford, P., 463
*Barroso-Moguel, R., 321
*Basset, G., 456
Batalla, E., 313
Bayles, T. B., 314
Bayliss, R. I. S., 124, 322, 460
Bean, W. B., 111
Beck, J. C., 124
Beckett, A. G., 125
*Beelar, V. P., 113
Ben, M., 324
Benichoux, P., 317
*Bennett, H. N., 310
Berkowitz, D., 305
*Berthier, L., 217
*Bertrand, A., 310
*Besson, F., 310
Besson, L., 121
Bettley, F. R., 116
Beyer, A., 219
Bilka, P. J., 451
*Binks, F. A., 118
*Biorck, G., 450
Bishop, C., 219
Bishop, J. M., 110
Bisyarina, V. P., 214, 309
*Blankenheim, H., 224
Blankenhorn, M. A., 317
Blockey, N. J., 119
Blumenfeld, S., 318
*Blumensaat, C., 455
Boas, N. F., 129
*Böni, A., 464
*Boesman, T., 114
Boling, L., 127
Bollet, A. J., 312
*Bonard, E. C., 119
Bongiovanni, A. M., 462
Bonmann, K. H., 452
Bonner, C. D., 323
*Bonnet, H., 310
*Bonola, A., 114
*Bopp, A., 456
*Bordier, P., 311
Bourel, M., 116
Bourne, G., 307
Bouvrain, Y., 305
Brachman, P., 314
Brain, R., 218
*Bramwell, C., 310
Bray, P. F., 222
Bricaire, H., 319, 458
Brockbank, W., 321 *bis*
*Brodie, B. B., 465
*Brodkin, H. A., 131
*Brous, M., 464
Browne, J. S. L., 124
*Browning, J. S., 465
Brunelli, M. A., 109
Bryson, K. D., 116
Buchan, J. F., 454
Bullock, J. A., 219
Bundick, W. R., 320
Bunim, J. J., 311, 312
*Bunn, W. H., 310
Burley, D., 114
*Burns, J. J., 465
Burrage, W. S., 130

Callow, R. K., 129
Campo, C., 447
Caramanian, M., 110, *110, 305, 307
*Cardell, B. S., 221
Carnes, W. H., 115
*Caroit, M., 321
Carryer, H. M., 130
Carter, Y., 309, 310
Cartesegna, F., 313
Cartwright, G. E., 125
Cary, S. K., 125
*Casolo, G., 221
*Castagnoli, M., 120
*Castaigne, A., 119
*Castelli, D., 123
Catanzaro, F. J., 448
Cates, J. E., 458
Cave, A. J. E., 314
*Cecchi, E., 318
*Cerda C, M., 120
Certonciny, A., 118
Chamovitz, R., 448
Chaptal, J., 447
*Chapuis, R., 114
Charleux, G., 130
Chatterjee, J. B., 221
*Chevallier, J., 456
*Chevéz, A., 321
*Chiti, E., 217
Clark, E. J., 109
*Clark, I., 463
Clarke, E., 322
Clautour, J., 316
Clifton, F., 454
Cochran, J. B., 126
*Coke, H., 456
*Colinet, E., 456
Collins, D. H., 453
*Conn, H. L., 110
Conn, J. W., 322
*Conner, S. K., 465
*Conterno, G., 110
Cooper, R., 322
*Cop, D., 455
Cope, C. L., 222
Corbelli, G., 109
Costa, F., *120, *455
Costa Bertani, G., *131, *224, *464
Coste, F., 116, *456, *463
*Costero, I., 321
*Courjaret, J., 121
Courrault, R., 308
Cowan, T. W., 218
Coyer, A. B., 455
Creveld, S. van, 448
Crisp, E. J., 464
Crittenden, J. O., 122
*Currie, J. P., 120
*Curwen, I. H. M., 455
Curzio, A., 221

Dagonet, Y., 308
Daneo, V., *123 *ter*, *221, 313
*Daniels, R. S., 310
*Danopoulos, E., 120
Danowski, T. S., 459
Daum, K., 111
*Davalli, C., 455
Davis, L. L., 307
*Davison, S., 217
Dawidowicz, A., 119
*de Azua-Dochao, L., 224
*Debeyre, J., 132
Debeyre, N., 311
*Delaude, A., 119
*Delaville, G., 114
*Delbarre, F., 463
Deltour, G., 319
*Denis, A., 131
Dent, C. E., 223
Derriks, R., 459
Desaulles, P., 129
*Desestres, —, 111
Desproges-Gotteron, R., 316
*Destefanis, E., 110
Destombes, A., 314
*Dias Velloso, G., 120
Dick, A. P., 125
*Dickgiesser, F., 221
*Dilallo, R., 450
di Matteo, J., 308
Dohan, F. C., 122
*Dolan, M. A., 450
Dombre, —, 130
Donald, K. W., 110
Done, A. K., 460
*Dresner, E., 314
*Drew, J. F., 224
*Drieux, H., 114
*Druckmann, A., 452
*Drudi, C., 456
Dubois, E. L., 117, *119
*Dubois, R., 450
Duff, I. F., *314, 450
*Dupré, A. L., 217
*Durman, D. C., 318
Duryee, A. W., 317

Eaton, J., 115
Eberlein, W. R., 462
*Edström, G., 110
Egelius, N., 322
Eik-Nes, K., 125, *324, 456, 461
*Einaudi, G., 123 *bis*
Eisler, M., 324
Elingshausen, H. P., 452
Elliott, R. H. E., 223
Ellis, F. A., 320
Ely, R. S., 222, 460
Engleman, E. P., 120, 215, 462
*Ensign, D. C., 318
*Enzinger, J., 131
*Epstein, N., 216
Eskin, I. A., 323
Espacio, L., 313
Esposito, M. J., 449
Eyquem, A., 121

Fabre, J., 127
*Fähndrich, W. H., 451
*Fairburn, D., 455
Fajans, S. S., 322
Fantuzzi, B., 449
Farr, C. H., 453
Favour, C. B., 314
Fearnley, G. R., 450
Feriozi, D., 124
Ferrand, M., 304
*Ferraris, F., 310
*Fessler, J. H., 123
*Feyrter, F., 464
Firor, W. M., 116
Fischer, F., 129
Fischgold, H., 454
Fisher, B. M., 127
*Fitting, W., 224
*Fleming, J. L., 318
Fletcher, E., 316, 451
Florentin, A. A., 461
*Forest, A., 119
Forestier, J., 112, 115, 118
*Fornara, P., 451
Forsham, P. H., 120
Fortin, P., 305
Fowlks, E. W., 318
Foz, A., 122, 133
*Fränkel, M., 452
*Frain, J. B., 120
Fraisse, J., 447
François, J., 312
Françon, F., *110, *121
*Françon, J., 121
*Franz, A., 120
Frazer, E. H., 318
Fredell, E. W., 462
Freeland, D. E., 118
*Freislederer, W., 221
*Fremont-Smith, P., 451
Fruchart, G., 314

Gabriel, J. B., 463
*Galli, G., 455
*Galloway, L. S., 221
Gamna, G., 306
Gamp, A., *119, *123, *456
Garcia-Llaurado, J., 222
*Gaudin, G., 217
Geller, P., 459
Gelli, G., 306
Gennes, L. de, 319, 458
Germain, D., 320
Geyer, S., 305
*Ghanem, M. H., 464
Gilbert-Dreyfus, —, 128
Gilgenkrantz, J. M., *216, 305
Gillespie, W. A., 109
*Gioanni, T., 111
Girard, C., 305
*Giraud, G., 310, 453
*Girerd, G., 216
Goldfien, A., 120, 461
*Goldstein, A. S., 318
Goldthwait, J. C., 314

*Goldwater, L. J., 224
Goldzieher, J. W., 459
*Gomez Orbaneja, J., 224
*Goodwin, S., 465
*Gospodinoff, A., 321
*Gould, I. D., 451
Goulding, R., 221
Gray, C. H., 123
Green, T. W., 120
Greene, M. H., 307
Greenman, L., 459
Greer, C. H., 454
*Gregoris, L., 456
Gribble, M. de G., 118
Griffiths, J. D., 314
*Gros, H., 456
Grosfield, H., 128
*Gross, D., 224
*Grubb, K. P., 111
Grumbach, M. M., 462
Guez, A., 460
Guillon, J., 319
*Gulotta, G. A., 310
*Gurling, K. J., 221
Gutner, L. B., 318
Gvelesiani, K. G., 309

Hässler, E., 215
*Halhuber, M. J., 465
*Hall, P., 450
*Harkness, A. H., 119
Harper, C., 223
*Harris, S. B., 464
*Harris, T. N., 110
Hart, F. Dudley, 114
Hart, M., 219
*Harter, F., 221
Hastrup, B., 129
*Haus, E., 465
Haustrate, L., 312
Haydar, N. A., 461
Heathfield, K. W. G., 217
*Hebbert, F. J., 110
Heffer, E. T., 107, 220 *bis*
Hellbaum, A. A., 219, 453
*Heller, G., 451
Hench, P. S., 458
Henderson, L. L., 130
Henneman, P. H., 130
Henriksen, E., 130
*Herbert, J. J., 114
Hess, P., 452
*Higgons, R. A., 450
Highton, T. C., 313
*Hiller, E., 465
Hilton, G., 315
*Hines, J. J., 111
Hodges, R. E., 111
Hollander, J. L., 122
Hollister, L. E., 215
*Hollmann, S., 123
Holt, K. S., 215 *bis*
Holzbauer, M., 457
Homburger, F., 323
*Horning, E. C., 465
*Horton, W. G., 455
Houghton, L. E., 459
*Houli, J., 120
Houser, H. B., 109
*Howard, L. D., 454
Hudson, B., 320
Hudson, P. B., 223
Hunter, J. D., 460
*Hunziker, H., 121
Huriet, C., *216, 305
*Hursh, L. M., 324
*Hussel, W., 318
*Hutchison, H. E., 123
Hyman, G. A., 223

Illingworth, R. S., 215
*Inama, K., 465
Irby, R., 310
Irwin, J. W., 130
*Isemein, L., 455
Ishmael, W. K., 219, 453

Jackson, R. L., 448
*Jackson, W. M., 318
Jacobs, A. L., 214
Jacobs, J. H., 316
*Jacobson, A. S., 451
Jacqueline, F., 121 *bis*
Jahn, J. P., 127
*Jarvinen, K. A. J., 451
Jawetz, E., 128, 459
Jean, R., 447
Jeffrey, M. R., 312
Jepson, R. P., 132
*Jewett, H. B., 318
Jochem, E., 121
Johnson, B. B., 458
*Johnson, G. C., 454
Johnson, H. P., 120, 462
Jones, D. E. A., 459
Jones, R. S., 309, 310
Jonsson, E., 322
Josephs, C., 112
Josserand, A., 320
*Jurmand, S.-H., 120
Juster, M., 454
Justin-Besançon, L., *114, *321

Katz, H. M., 463
Kelley, V. C., 222, 460
Kellgren, J. H., 119
Kelly, H. G., 448
Kelly, M., 112
Kendall, P. H., 464
*Kibler, M., 114
*King, R., 114
Kinsell, L. W., 127
*Kirnberger, E. J., 456
Klein, R., *132, *464
Klotz, H. P., 460
*Knobová, J., 131
Knowles, H. C., 317
*Kobes, H. R., 217
Koelsche, G. A., 130
*Kofman, S., 454
Kolb, F. O., 215
*Kolodny, M. H., 451
Krautzun, K., 452
*Krewer, B., 113
Kroop, I. G., 107, *111, 220 *bis*
Krupp, M. A., 120, 462
*Kruskemper, H. L., 465
Kuhns, J. G., *114 *bis*, *218, *224
Kuipers, R. K. W., 118
*Kukowka, A., 321
*Kulonen, E., 456

Labesse, J., 308
*Lacapère, J., 114, 117
Lackner, R., 450
Lacrosaz, —, 130
Lafargue, J., 128
Laidlaw, J. C., 461
*Laine, V., 451
Landing, B. H., 124
Langeron, L., 314
Lansbury, J., 111, 311
Larcan, A., *216, 305 *bis*
*Laroche, C., 121
*Latour, H., 310
Layani, F., 310
Leathem, J. H., 324
Leb, A., 464
Lebeurre, R., 132
*Lebon, J., 451
LeBrie, S. J., 324
Lederer, J., 459
*Lee, P. R., 114
*Leikola, E., 454
Leinwand, I., 317
Leitner, Z. A., 214
Lemaire, E., 314
*Lenoch, F., 131
Leovy, W. A., 127
*Lepow, I. H., 451
Leu, H. J., 216, *464
*Levy, A., 310
Lévy, R., 113
Lièvre, J. A., 454
Likoff, W., 305
Lindahl, A., 113
*Lindholm, R. V., 114
Lloyd, J., 129
Lloyd-Roberts, G. C., 314
*Long, C., 318
Long, D. A., 129
*Lopez, B., 224
Lorber, J., 215
Lorch, P., 113, *113
*Lovgren, O., 463
*Lowman, E. W., 114
Lucherini, T., *120 *bis*, *318
Luetscher, J. A., 458
Luger, N. M., 463
*Luisada, A. A., 216
Lumpkin, W. R., 116
Lunnon, J. B., 123
Lutterbeck, H., 220

*McCarty, M., 216
McCauley, H. B., 224
McClure, F. J., 224
McDonald, I., 452
McEwen, C., *216, 311
McGehee, E. H., 123
McGrath, A. K., 462
Mach, R. S., 127
Mackenzie, K. R., 124
*McKusick, V., 450
MacLean, K., 119, 123, 221
MacLeod, M., 110
*Maffei, G., 321
*Maggi, C. A., 221
*Maher, J. A., 123
Mainland, D., 319
Mak, G., 448
*Makinen, P., 456
*Mangelson, F. L., 221
Mannes, P., 459
Marchand, J. H., 316
*Marks, G. H., 451
Marquezy, R. A., 308
*Mars, G., 114
Marshall, J., 131
*Martorelli, J., 218
Mason, H. L., 458
Massell, B. F., 458
*Massin, M., 119
*Mastragostino, S., 114
*Masturzo, A., 464
Mathieu de Fossey, B., 319
Mattox, V. R., 458
Maxwell, R., 324
May, F., 218
*Mayerhofer, E., 114
Meagher, T. R., 127
Medical Research Council, 112, 448
Meier, R., 129
*Melissinos, K., 120
Menkin, V., 457
Merrill, E. R., 459
Michaud, P., 115
Michel, J., 454
*Michotte, L., 454
*Mikkelsen, W. M., 314
*Miller, S., 114
Miniconi, P., 304
*Mintz, B., 224
Miowski, D. K., 126
Mittelman, A., 223
Monier, H., 117
Moore, F. D., 461
Moore, T., 214
*Moreau, C., 132
Morel, F., 116
*Moreno, B. A., 224
Morin, G., 317
Morris, A. J., 448
*Morris, J. E., 120
Mozziconacci, P., 110, 307
*Murley, A. H. G., 118
Myrden, J. A., 461

Nabarro, J. D. N., 222
*Natale, P., 120
*Naylor, A., 455
Needham, C. D., 452
Nelson, D. H., 125, *324, 456
Neuhaus, C., 449
*Neustadt, D., 120
*Neuwirth, E., 114
*Newman, M. K., 318
Newns, G. R., 112, 450
Nicaise, R., 459
Nogueira Cardoso, M. A., 214
*Norman, A., 463
Nouaille, J., 110
Nuffield Foundation Joint Committee on Cortisone, ACTH, and Other Therapeutic Measures in Chronic Rheumatic Diseases, 112
Nussenzveig, I., 214
Nussenzveig, V., 214

O'Connell, P. A., 458
*d'Oelsnitz, M., 111
*Offret, G., 119
*Ogston, A. G., 123
*Oswald, H., 123

*Padovani, J., 455
Page, F., 116
Palich-Szántó, O., 119
Palmer, J. G., 125
*Paolaggi, J., 121
Papagni, L., *120, *455
Paris, J., 125
Pasquariello, G., *310, *321
Pasquet, P., 304
Pasquet, V., 304
*Paton, M. D., 454
Patrick, D. R., 219
Paul, W. D., 111
Payne, R. W., 219, 453
*Peabody, C. W., 314
Pechet, M. M., 312
Perry, C. B., 109
Perry, W. D., 448
*Peterman, E. A., 221
Peters, G. A., 130
*Petersén, I., 451
Peterson, H. H., 127
*Peterson, W. L., 310
Petry, H., 216
*Petty, H., 314
Peyron, J., 310
Philpot, G. R., 223
Pietruschka, G., 224
*Pilorgé, D., 216
Pimenta de Campos, E., 214
*Pinheiro Martins, A., 120
Piñol, J., 311
Podberezec, M., 223
*Pohl, W., 224
*Poli, M., 110
Polley, H. F., 458
Poole, E. W., 131
Postel, M., 315
Poujade, L., 308
Power, M. H., 458
Prickman, L. E., 130
Pridie, K. H., *217, *315
Prosperi, P., 127
*Puech, P., 310

*Quin, C. E., 118

Ragan, C., 128
Raile, R. B., 222
*Raleigh, G. W., 217
Ramadier, J. O., 315
Rammelkamp, C. H., 448
*Rankin, J., 110
Rankin, J. de W., 309
Ratschow, M., 464
*Ravault, P., 217
Rawls, W. B., 459
Raynaud, R., 304
Reale, A., 305
*Reichenthal, J., 465
Reiman, J., 463
Rendle-Short, J., 215
Renold, A. E., 461
Reynard, W. A., 131
*Rezzonico, G., 224
*Rhodes, P. H., 310
Rich, H., 308
Richards, D. G., 224
Richards, M. T., 114
Richardson, E. M., 122
Richter, M. N., 317
*Riddell, M. J., 454
*Ritama, V. V., 451
Rivano, R., *217, *221, *318
*Rivera, M. E., 451
Robecchi, A., *221, 313, *454
Robert D'Eshougues, J., 304
*Roberts, E., 110

Robinson, H. M., 126
Robinson, H. S., 119
Robinson, J. J., 108
Robinson, R. C. V., 126
Robinson, W. D., *314, 450
Robson, J. M., 221
Rössing, P., 220
Rogan, M. C., 452
Rogers, F. B., 311
*Rogoff, B., 114
Rose, F. C., 316, 451
*Rose, G. K., 451
*Rose, R. K., 465
Ross, D. N., 120
Rossi, R., 127
Rotés-Querol, J., 311, *316
Routh, J. I., 111
*Roux, J., 310
*Roversi, A. S., 114
Roy, A., 458
Rubbiani, V., 115
*Rubens-Duval, A., 321
Ruebner, B., 122
*Ruiz Moreno, A., 219
*Rulfo, J., 310
Russek, A. S., 463
*Rutstein, D. D., 310

Salassa, R. M., 125
*Salazar-Mallen, M., 310
Salomon, L., 221
Samuels, L. T., 456, 461
Sandberg, A. A., 125, *324, 456, 461
Saslaw, M. S., 307
Savidge, R. S., 321 *bis*
Scalabrino, R., *310, *321
*Scheidegger, J. J., 119
*Scheuer, F., 114
Schiavetti, L., *310, *318
Schiller, J., 128
*Schimmel, A., 114
Schlossmann, K., 121
*Scholz, H., 224
Schreiner, B., 113
Schrub, J., 308
*Schubert, R. R., 224
*Schumacher, H., 464
Schweitzer, M., 447
Scopinaro, D., *217, *318
Scow, R. O., 129
Scull, E., 319
Seifert, H., 122
Selye, H., 123, 462
*Sérane, J., 121
*Serre, H., 316
Sèze, S. de, *120, *131, *132, 311, *455 *bis*
Shackman, N. H., 220 *bis*
Sharman, I. M., 214
Shatton, J., 319
*Shenkin, H. A., 219
Shetlar, M. R., 219, 453
*Sigler, J. W., 318
Simson, J., 319
*Sitzerman, B., 314
*Sklar, M., 463
Slater, S. R., 107
Slocumb, C. H., 458
Smith, A., 319
Smith, E. M., 450
Smith, M. J. H., 123
Smith, R. T., 324
Sokolova-Ponomareva, O. D., 214, 309
Solari, S., *217, *221, *318
Soloff, L. A., 449
*Somer, P. de, 321
Sonntag, R., 214
Sors, C., 321
Soulié, P., 305
*Spence, M. P., 451
Sprague, R. G., 125
*Stadtsbaeder, S., 321
*Stanier, J. E., 123
Steenburg, R. W., 461
*Steffen, C., 224
Steiger, W. A., 125
*Stein, H., 114
Steinbeck, A. W., 124, 460
*Steinbrocker, O., 120
Stephantschitz, G., 113
Stetson, C. A., 448
*Stewart, J. M., 455
*Stoeber, E., 221
Stollerman, G. H., *216, *310, *450
Stolzer, B. L., 109, 448
Stoner, H. B., 323
Stoppelman, M. R. H., 448
Strauss, H., 305
Streitfeld, M. M., 307
*Strong, J. A., 454
Stronk, M. G., 448
*Suarez, R. M., 456
*Saurez, R. M., Jr., 456
Sulzberger, M. B., 130
Sundblad, L., 320, 322
Svartz, N., 121, *451
*Swineford, O., 465
Swingle, W. W., 324
Sylvestre, L., 119

Taber, K. W., 463
Tadzer, I. S., 126
Talbott, J. H., 219
*Tatum, J. C., 217
Tawil, G. S., 456
Teilum, G., 113
Teixeira, M. A., 124
Thévenoz, F., 112
Thill, A. E., 127
Thomas, G., 107, 127
Thomas, L., 324
Thorn, G. W., 461
Thoyer-Rozat, —, 128
*Thune, S., 456
Tichner, J. B., 459
Tichy, H., 122
Tidwell, R. A., 107
Toone, E. C., 310
*Toussaint, J., 217
Tranchesi, B., 214
Traverse, P. M. de, 121
Traynor, M. V., 130
*Trevathan, R. D., 217
Trocme, Y., 321
*Truedsson, E., 456
Truelove, S. C., 126
*Tufts, M., 217
Turin, R. D., 107
Turner, L. W., 111
Tyan, E. A., 128
Tyler, F. H., *324, 456, 461

Upson, M., 125

*Vainio, K., 451
*van der Meer, C., 114
Van Leeuwen, G. J., 448
*Van Slyck, E. J., 113
Van Wyk, J. J., 462
*Vartia, K. O., 454
Vaughan, J. H., 314
Vecchi, G. P., 115
Verhaeghe, A., 132
Vial, G., 117
*Vieira, J. A. N., 115
Viergiver, E., 108
*Vignon, G., 121
Vilanova, X., 311
*Vilaseca, J. M., 115
Villiaumey, J., *321, 458
Vincent, E. H., 132
*Violle, P. L., 121
Vogl, A., 318
Vogt, M., 457
*Vorlaender, K. O., 224

Wade, O. L., 110
*Wall, P., 318
Wallace, H. M., 308
Wallis, A. D., 108
Walter, J. B., 459
*Walthard, K. M., 218
Wang, D. M. K., 130
Ward, L. E., 458
*Warter, P. J., 120
Watkins, M., 114
Watson, D., 312
*Wedum, B. G., 310
Weigand, F. A., 459
Weil, M. H., 451
Weismann-Netter, R., 113, *113
*Weiss, T. E., 451
*Weitz, W., 450
*Welfling, J., 120
Wellič, J., 218
Welsh, A. L., 117
West, H. F., 112, 450
Whiteley, H. J., 323
Whiteley, M. M., 314
*Wilcox, E. B., 221
*Wilhelmi, G., 120
Wilkins, L., 462
*Willcox, P. H., 216
*Wille, E., 123
Williams, J. R. B., 217
Wilson, G. M., 461
Wilson, M. G., 447
*Winblad, S., 110
Winn, J. M., 453
*Winqvist, G., 463
Wintrobe, M. M., 125
Witten, V. H., 130
Witts, L. J., 126
Wolf, R. C., 324
Wolfson, W. Q., 455
*Wood, H. F., 216
*Wood, J. C., 110
*Wood, P., 221
*Wornom, P. H., 465
Wright, J. K., 119
*Wyss, S., 131

*Young, I. I., 463

Zacco, M., 122
Zarafonetis, C. J. D., 125
Zatuchni, J., 449
*Zeldis M. A., 120
Ziff, M., 311, 319
Zilli, A., 306
*Zimmerman, H. J., 454

Mrs Colby — file for ref VB

Urtication by switching with the common stinging nettle appears to have been an old Roman custom. When Julius Cæsar landed, his soldiers had with them nettle seeds which they sowed for their own use as an epidermal stimulant and counter-irritant, to relieve stiffness and rheumatism caused by the already then notorious British climate.

The Modern Answer to an Ancient ill . . .

combined systemic and local anti-rheumatic therapy

arthripax tablets

formula Mephenesin 1 gr. Salicylamide 5 grs. Dihydroxyaluminium Glycinate 1½ grs.

Effectively relieves pain and spasm and reduces inflammation associated with rheumatic conditions. Negligible incidence of side-effects as synergy permits minimal dosage of mephenesin and salicylamide. Dihydroxyaluminium glycinate minimises the possibility of gastric disturbances.

dosage 2-3 tablets t.d.s. **Basic N.H.S. cost** 50 tabs. 3/4d. plus 10d. P.T.

arthripax cream

formula Glycol Salicylate 7.50% Ephed. Hydrochlor. 0.50% Benzyl Salicylate 7.50%
Menthol 1.00% Terebene 7.50% Capsicin 0.05%

Rapidly penetrates the epidermis through the pilo-sebaceous glands, producing local hyperaemia with prompt and prolonged local analgesia, relieving pain, spasm and inflammation. Negligible risk of untoward skin reactions.

directions 2 applications daily normally suffice. **Basic N.H.S. cost** 1 oz. 1/5d. plus 5d. P.T.

Not advertised to the public ● **Professional samples and literature on request**

CLINICAL PRODUCTS LTD., RICHMOND, SURREY

Preference, Purdue Pegboard, and others as indicated.

With this initial data, the social worker and the psychologist discussed the patient's problems from a initial decisions were subject to review during hospitalization, and weekly staff meetings were held to co-ordinate reports on behaviour and progress.

RELIEF OF PAIN
HYPERAEMIA
RELAXATION

Response to the percutaneous stimulation of warmth with

FINALGON OINTMENT

in rheumatic and neuralgic conditions

tube of 20 g

LEWIS LABORATORIES LTD., LEEDS 9

ASPIRIN INTOLERANCE IN RHEUMATOID ARTHRITIS

BUFFERIN-

THE NEW BETTER TOLERATED ANALGESIC

MOST SUCCESSFUL ANSWER YET DISCOVERED

Following last year's report[1] by the Joint Committee of the Medical Research Council and Nuffield Foundation, many practitioners have returned to aspirin therapy in place of cortisone. Effective therapy with aspirin and similar salicylates unfortunately has been hampered by the problem of gastric irritation, which affects as many as 42% of arthritic patients. Bufferin, the new analgesic which reduces gastric intolerance to a negligible minimum, is the most successful answer to the problem yet discovered.

BUFFERIN FAR BETTER TOLERATED BY ARTHRITICS

Bufferin combines acetylsalicylic acid with the antacids aluminium glycinate and magnesium carbonate (gentle buffering acids which do not produce "acid rebound"), and is well tolerated even by arthritics. In blind trials amongst arthritics with proven intolerance to ordinary aspirin, 70% had no gastric symptoms after taking large doses of Bufferin over periods of 4 to 16 months.[2] Previous studies amongst the general population showed that only 1 patient out of 238 had any distress after taking 10 grains of Bufferin.[3]

ACTS TWICE AS QUICKLY AS ASPIRIN

Not only is Bufferin better tolerated by the stomach than ordinary aspirin, but its pain relieving ingredient is absorbed twice as quickly into the blood stream. Trials show that on an average the 10-minute salicylate level after taking Bufferin was more than 20% higher than the 20-minute level after taking ordinary aspirin.[3]

NO EQUIVALENT IN BRITISH PHARMACOPOEIA

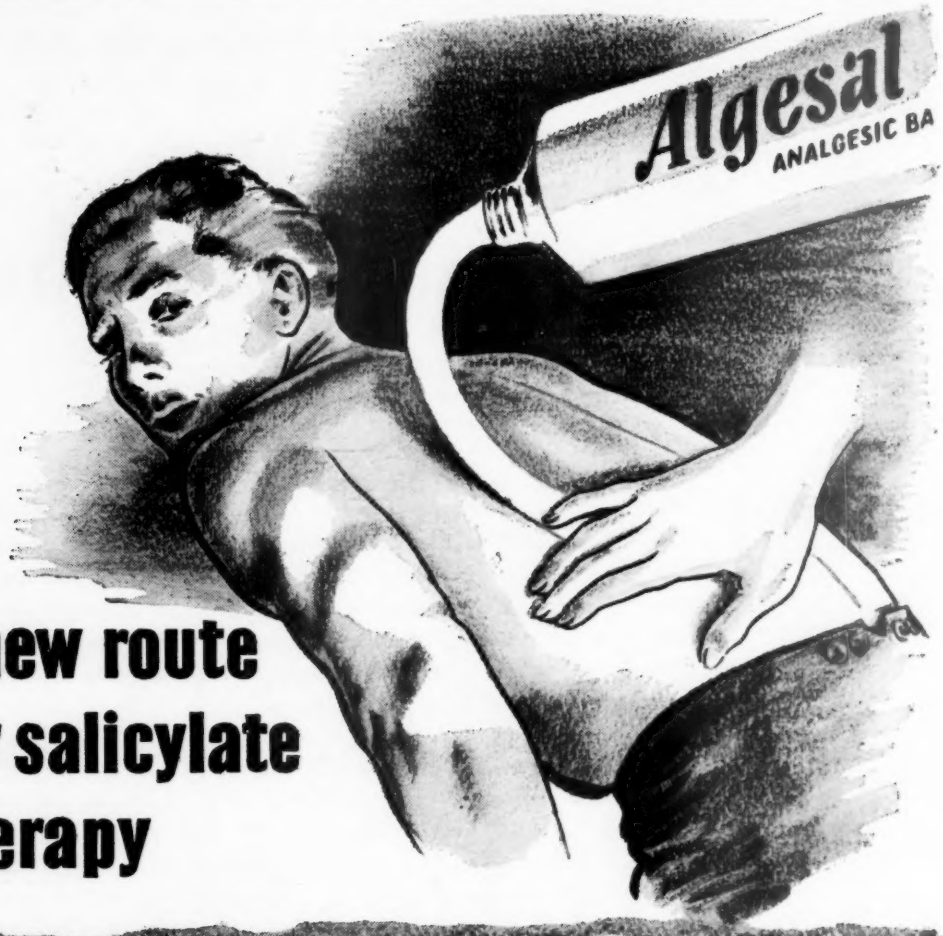
Bufferin is unique in incorporating aluminium glycinate and magnesium carbonate as buffering agents and has no equivalent in the British Pharmacopœia or National Formulary. This fully justifies the prescription of Bufferin on E.C.10.

References: 1. British Medical Journal, 1954, 1 : 1223. 2. Journal of the American Medical Association, June 4, 1955, P. 387. 3. J. Amer. Pharm. Assoc., 1950 39 : 21.

Further information : A detailed, fully documented leaflet and sample available on request to the makers, Bristol-Myers Co. Ltd., Dept. D, 211 Blackfriars Road, London, S.E.1.

BUFFERIN TRADE MARK
ANTACID ANALGESIC

Formula: Acetylsalicylic Acid 5 gr. : Aluminium Glycinate ¾ gr. : Magnesium Carbonate 1½ gr.



A new route for salicylate therapy

Algesal balm has only one active principle, the newly-synthesised compound, diethylamine salicylate, which differs from other salicylates in that it is *not* a counter-irritant nor a rubefacient.

Diethylamine salicylate has been shown to penetrate the skin in significant quantities and this discovery has opened up a new route for salicylate therapy.

The site of action of salicylates taken by mouth is still not known for certain and some authorities suggest that it may be peripheral, at the site of the pain[1]. Percutaneous salicylate therapy thus has immense possibilities, and Algesal is proving to be a most valuable remedy for the relief of local tissue pain by inunction.

The indications for Algesal fall naturally into three groups: rheumatism, pain following trauma of different kinds, and certain painful conditions of unknown aetiology—e.g. chilblains and idiopathic night cramps.

Algesal is a non-staining white cream with a pleasant smell of lavender. It contains 10% diethylamine salicylate, in a vanishing cream base specially formulated to assist skin penetration.

Samples and literature will gladly be sent on request to the manufacturers, E. G. H. Laboratories Ltd., Peru Street, Adelphi, Salford 3.

[1] Practitioner, (1953) 170, 515.

Algesal

E.G.H. LABORATORIES LTD., PERU ST., SALFORD 3, LANCS

INTRAMUSCULAR IRON

Widespread Acceptance...

"The iron given parenterally was absorbed from the intramuscular site and utilised." [1]

"Utilisation for haemoglobin production was extremely good." [2]

"In every patient a satisfactory rise in the haemoglobin took place." [3]

". . . all the patients in the series developed a vigorous sense of well-being which contrasted very strikingly with their previous chronic ill-health." [3]

"From the present series it appears that this new iron-dextran complex is a notable advance in the treatment of the iron-deficiency of pregnancy." [4]

1. LANCET. 1954, 2, 942.
2. B.M.J., 1954, 2, 1257.
3. B.M.J., 1954, 2, 1255.
4. LANCET, 1954, 2, 1245.

IMFERON IS THE FIRST EFFECTIVE IRON PREPARATION FOR INTRAMUSCULAR INJECTION

IT PROVIDES the rapid, reliable response of an order hitherto only obtainable with intravenous preparations; and it takes much less time to administer.

IMFERON IS indicated for the patient who is refractory to, or intolerant of, oral iron; and when a rapid response is required, as in anaemia of pregnancy.

TECHNIQUE

"IT WAS OBVIOUS during this study that the skill and care of the person giving the injections does much to minimise local discomfort and staining, and it is significant that only two patients failed to attend for further injections." (LANCET, 1954, 2, 1245).

AMPOULES *2 ml. (100 mg. Fe) boxes 10 and 100*
AMPOULES *5 ml. (250 mg. Fe) boxes 5 and 50*

FULLY-DESCRIPTIVE LITERATURE, including dosage Calculator, on request. A Technical Information Service is at your disposal.

IMFERON IRON-DEXTRAN COMPLEX
TRADE MARK

A BENGER PRODUCT

BENGER LABORATORIES LIMITED · HOLMES CHAPEL · CHESHIRE

I.5.

Transvasin

brings the esters of NICOTINIC ACID SALICYLIC ACID p-AMINOBENZOIC ACID

to the focal point of soft-tissue rheumatism

The esters in Transvasin, a new preparation developed by Hamol S.A., our Swiss associates, readily pass the skin barrier in therapeutic quantities and enable an effective concentration of the drugs to be built up where they are needed.* Transvasin not only induces vasodilation of the skin with a superficial erythema, but also brings about a deep hyperaemia of the underlying tissues. It is non-irritant, and can be safely used on delicate skins.

It is now being widely prescribed, with successful clinical results. Since a very small quantity is sufficient for each application, the cost of treatment is extremely low.

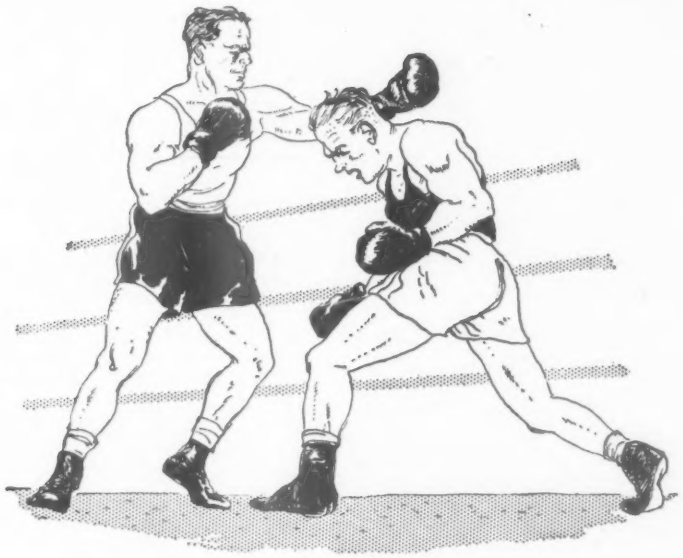
Salicylic acid tetrahydrofurfuryl-ester	14%
Nicotinic acid ethyl-ester	2%
Nicotinic acid n-hexyl-ester	2%
p-Aminobenzoic acid ethyl-ester	2%
Water-miscible cream base ad	100%

Transvasin is available in 1 oz. tubes, basic price 2/6 plus 9d P.T., and is not advertised to the public. Samples and literature will be gladly sent on application.

* *Therapeutische Umschau VIII*, 1952, 10, 143

LLOYD-HAMOL LTD., 11 Waterloo Place, London, S.W.1 WHItehall 8654/5/6

Transvasin is the registered trade mark of Lloyd-Hamol Ltd.



Unfortunately, the pursuit of the noble art is unthinkable amongst those with even the mildest rheumatic distress. But to the uncounted thousands who suffer from recurrent ' fibrositis,' ALGIPAN Balm provides the counter-cross to pain. The in-fighting qualities of *histamine* and *methyl nicotinate* ensure penetration well below the skin, inducing an immediate capillary and arteriolar dilatation which adroitly sidestep the lunges of muscular rheumatism.
ALGIPAN is available in 40 G. tubes.

'ALGIPAN' Balm

TRADE MARK

Wyeth

JOHN WYETH & BROTHER LIMITED, Clifton House, Euston Road, London, N.W.1

Who's next?

Another rheumatic sufferer?

It is fortunate that an effective adjuvant in the treatment of this disease is available, bringing the patient prompt and effective relief from pain.

The value of salicylate in rheumatic disorders has long been recognised, but until recently its use was restricted by the toxic effects accompanying the necessarily high dosage.

In Berex, the combination of acetylsalicylic acid and calcium succinate enables toleration of massive aspirin dosage without lowering the prothrombin level, with encouragement of tissue respiration, and with less gastric disturbance.

SUMMARY OF STUDY ON SUCCINATE-SALICYLATE THERAPY*

A succinate-salicylate combination was found superior to acetylsalicylic acid in rheumatic states both on grounds of therapeutic efficacy and lower toxicity. Adequate amounts of the former could be administered with more lasting effect and with fewer and milder side effects. Furthermore, succinate-salicylate affects the disease process itself, as well as relieving painful symptoms and does not abnormally increase prothrombin time even after prolonged dosage.

* *Delaware State Medical Journal* (1954) **26**, 22.

BEREX
Trade Mark

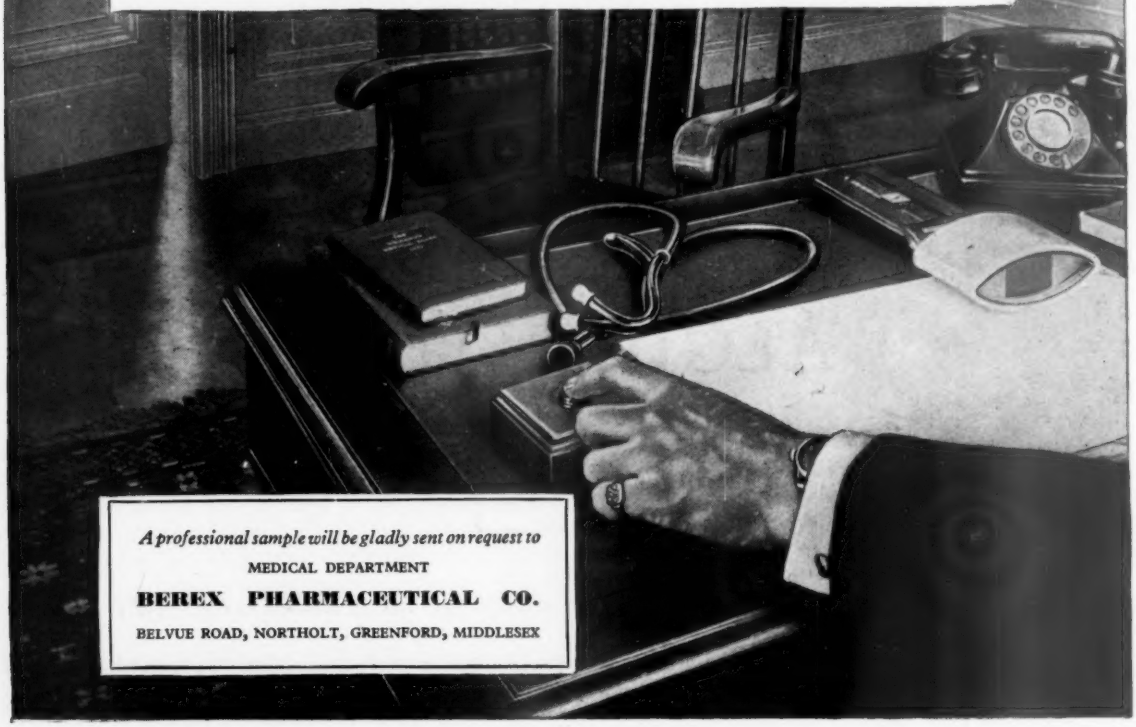
SUCCINATE-SALICYLATE THERAPY

For the relief of the painful symptoms associated with all rheumatic disorders

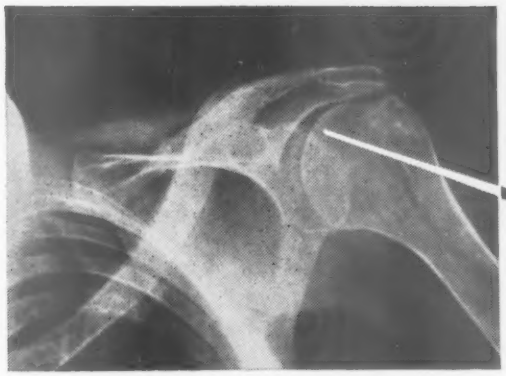
FORMULA: *Calcium Succinate 2.8 gr.*
Acetylsalicylic Acid 3.7 gr.

IN TABLET FORM: *Basic N.H.S. Price 4/8½d.: 100 tablets.; 24/3d.: 600 tablets.*

BEREX *has never been advertised to the public*



A professional sample will be gladly sent on request to
MEDICAL DEPARTMENT
BEREX PHARMACEUTICAL CO.
BELVUE ROAD, NORTHOLT, GREENFORD, MIDDLESEX



PARTICULARLY FOR AFFECTED JOINTS

Butazolidin
REGD. TRADE MARK.
Geigy

Many cases of rheumatoid arthritis and osteoarthritis have been successfully treated with small doses of Butazolidin. Easement of pain is usually experienced after only a few days of treatment, and the extra movement of affected joints obtained is often greater than can be accounted for by analgesia alone.

Included in schedules 1 and 4 of the Poison Regulations, Butazolidin is prescribable on N.H.S. Form E.C.10 and is available in the form of

Geigy

TABLETS containing 100 mg. in containers of 50, 250 and 1,000 tablets; and containing 200 mg. in containers of 20, 50, 100 and 500 tablets.

AMPOULES of 1,000 mg. in 5 ml. of injection solution in boxes of 5, 25, 50 and 100 ampoules.

Detailed literature available on request.

GEIGY PHARMACEUTICAL COMPANY LTD.
Rhodes, Middleton, MANCHESTER

PH.75a

In Rheumatic Disease

when intensive salicylate therapy is contemplated

consider

SODIUM GENTISATE

GABAIL

in tablets 0·5 G

The sodium salt of 2:5 dihydroxybenzoic acid—an oxidation product of salicylate metabolism and an antirheumatic of high therapeutic activity.

SODIUM GENTISATE (Gabail) gives results similar to large doses of salicylate, with however—

- **NO gastric irritation**
- **NO increase in prothrombin time**
- **NO tinnitus or aural symptoms**
- **NO lowering of alkaline reserve**

High plasma concentrations are easily reached and maintained

Details and clinical sample from the distributors :

THE ANGLO-FRENCH DRUG Co. Ltd. 11-12 Guilford St. London, W.C.1

★

For **OVER-ACIDITY** *prescribe*

VICHY CELESTINS

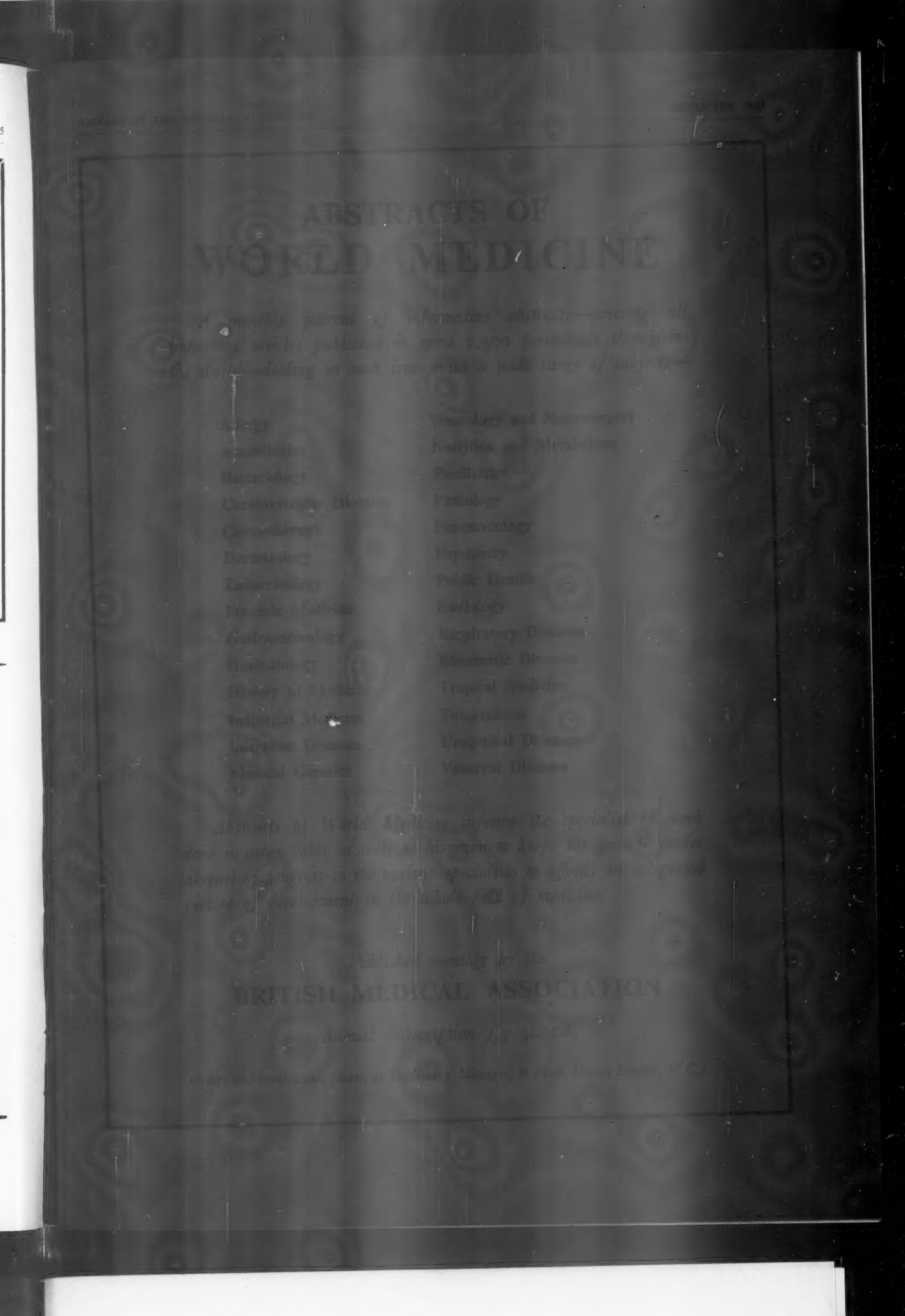
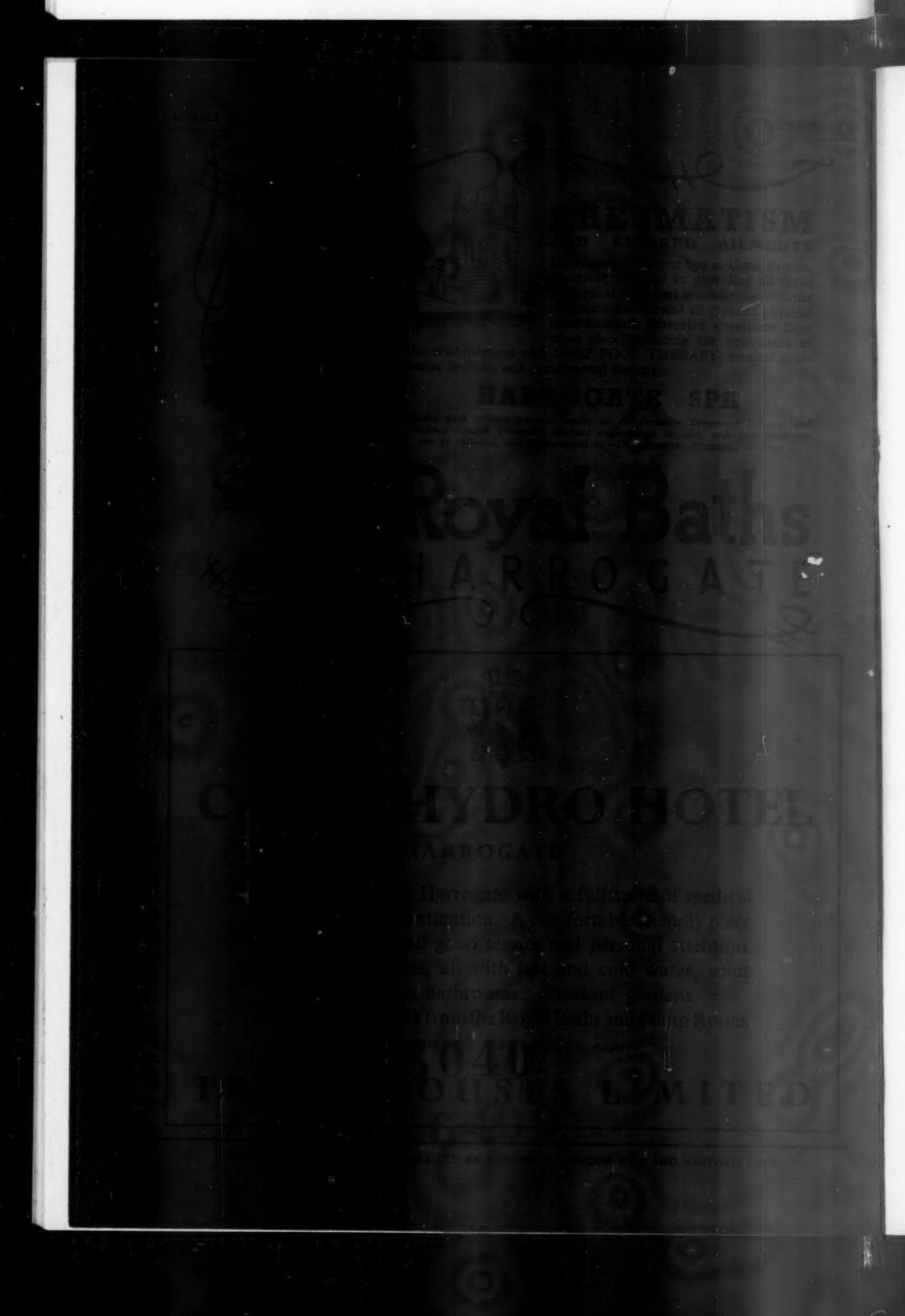
WORLD-FAMOUS FRENCH SPA WATER

Bottled as it flows from the Spring

Holding an undisputed place in the therapeutics of rheumatism and arthritis, as well as in disorders of the digestive and urinary tract, Vichy-Celestins is invaluable to sufferers from these ailments.

Sole Agents in the United Kingdom:

INGRAM & ROYLE LIMITED

50 Manchester Street, London, W.1

★